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ESTROGEN-PROGESTERONE THERAPY: A NEW APPROACH IN THE TREATMENT OF HABITUAL ABORTION*

Studies Indicating Its Rationale in 24 Treated Cases

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Introduction

MANY causes for habitual abortion and miscarriage are known or have been postulated. Among these are abnormalities of the ovum resulting from defects inherent in the germ plasm; maternal factors which influence pregnancy, such as inflammatory disease or tumors of the pelvic organs, febrile diseases, maternal syphilis, malnutrition, avitaminoses, incompatibility of blood types (particularly of the Rh factor), thyroid dysfunction and deficiencies of the hormones produced by the corpus luteum and the placenta during pregnancy; external factors, such as chemical poisoning, x-ray and radium, and trauma; abnormalities of the male germ plasm and constitutional diseases of the male. In the past the study of many such patients who have repeatedly aborted or miscarried has resulted in failure to find in a great majority of them any etiological factor which could be incriminated with certainty. This strengthened the belief commonly expressed that abnormalities inherent in the germ plasm constitute the largest cause for spontaneous abortion, particularly since it had been shown by a number of observers[1-4] that a high percentage of aborted embryos are pathologic. As pointed out by Meaker[5] this concept has lost considerable support in view of the demonstration that many of these pregnancies can be saved and carried to term with the birth of normal babies, confirming the viewpoint of Mall[1] that these malformations may often result from external factors which have interfered with the growth, development, or nutrition of the embryo.

Much emphasis has been placed in recent years on the importance of endocrine factors in abortion; particularly those relating to functional failure of the corpus luteum and placenta. A sufficient number of studies are now available from a number of laboratories to indicate that abortion is sometimes preceded by

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a marked fall in pregnandiol levels, pointing toward premature failure of the corpus luteum or inadequate function of the placenta.[6-9] On the other hand there are also a number of reports that in some normal pregnancies low pregnandiol titers have been encountered while other patients may threaten to abort when pregnandiol titers are normal.[6, 9] Finally, there are the therapeutic results with progesterone; like so many statistics on the treatment of abortion they are impossible of evaluation except to point out that they are conflicting.

In studies which we have made over a number of years on the blood and urine hormonal levels of normal and abnormal pregnancies, we have been impressed not only by the high percentage of habitual aborters who exhibit low pregnandiol titers but even more by the frequency with which these are associated with diminished blood and urine estrogen levels. Since both of these hormones are believed to be made by the corpus luteum during early pregnancy, these findings would support the diagnosis of premature failure of this structure; but since this same type of double deficiency was often noted by us after the first trimester, we were led to believe that the placenta can be equally responsible for the failure to produce estrogen and progesterone. These findings have encouraged us during the past three years to treat our habitual aborters with combined estrogen-progesterone therapy, despite early misgivings which we had concerning the administration of estrogens to patients who were threatening to abort or miscarry. During this time there appeared a report by Hamblen[6] that progesterone alone failed to elevate low pregnandiol titers and to prevent abortion and that in a few cases the addition of estriol glycuronidate did not help. More recently Hamblen[7] states, "We believe that 'synergism' of progesterone with estrogen is advisable," and has employed it in the treatment of abortion.

Clinical and Laboratory Data

Patients.—The present study was made on a group of 24 women seen by us during the past three years in whom the previous two or more pregnancies terminated in abortion or miscarriage. These patients had gone through a total of 80 previous pregnancies (Table I) from which there had resulted only seven (9 per cent) full-term living infants, despite various types of treatment in many of the pregnancies. There were 52 abortions, 18 miscarriages, and one premature baby which lived only a few minutes. Twenty of these 24 women had no living babies. Eleven women were pregnant for the third time, 7 for the fourth time. In one patient seven previous pregnancies had resulted in abortion at the eighth to tenth weeks. One patient pregnant for the twelfth time had two living children, 5 abortions, and 4 miscarriages.

TABLE I. OBSTETRIC HISTORIES

Total number of patients			24
Total number of previous pregnancies			80
Abortions	52		
Miscarriages	18		
Stillbirths	2		
Premature live births (did not survive)	1		
Full-term live births (all normal)	7		
Para 0 = 20		Grav iii =	11
Para i = 2		Grav. iv =	7
Para ii = 1		Grav. v or more =	6
Para iii = 1			

The ages of these patients ranged from 21 to 36 years. Fourteen women were less than 30 years of age.

A detailed analysis of the family and past medical histories of these patients did not reveal any factors which might be of etiological significance. There were no instances in which habitual abortion or miscarriage occurred in the mother or in sisters. No patients were included in this study who had pelvic tumors or other local abnormalities which might influence abortion, miscarriage, or premature labor.

Menstrual History and Fertility.—The menstrual histories of these patients were remarkably good (Table II) and compare favorably with those in similar groups of normal women. In 17, or 71 per cent, of the cases no marked deviation from normal was recorded. In 6 cases, episodes of hypermenorrhea, oligomenorrhea, or short periods of amenorrhea had occurred and one patient had a mild degree of menorrhagia.

From the standpoint of fertility (Table II) 13, or 54 per cent, of this group were able to become pregnant each time in less than six months and were classified as being of "good fertility."

TABLE II. MENSTRUAL HISTORY AND FERTILITY

	NO.	%
Normal menstrual history	17	71
Menstrual irregularity	6	25
Menorrhagia	1	4
Good fertility	13	54
Impaired fertility	2	8
Poor fertility	9	38

Two patients required from six months to a year to become pregnant and were classified as of "diminished fertility," while 9 patients were considered to be of poor fertility because they required more than a year for each conception; 4 of these patients had been under treatment as sterility problems. The percentage of patients with some impairment of fertility was probably somewhat higher in this group than average. There was, however, no correlation noted between degree of fertility and tendency to habitually abort. The patient with seven abortions had been married less than three years.

Studies Prior to the Present Pregnancy.—Fifteen of the 24 patients were seen before the present pregnancy began. In addition to careful physical examination the following studies were made on these patients in as many instances as possible: Wassermann; Rh factor; basal metabolism; sounding of the uterine cavity, study of the endometrium obtained by endometrial biopsy or by dilatation and curettage; urine hormone assays including gonadotropins, estrogens, and pregnandiol. In the husband, the basal metabolism, Rh test, and a semen study were made. In the 9 patients who were already pregnant some of these studies had previously been made. Many of these tests, particularly the basal metabolism and hormone assays were repeated during pregnancy.

Wassermann: The Wassermann and Kahn reactions were negative in all 24 of these cases and were also found to be negative in all of the husbands. There was no history of antisyphilitic therapy in any of the patients.

TABLE III. STUDIES PRIOR TO PREGNANCY: BASAL METABOLIC RATE
(Average of two or more tests)

	NO.	PERCENTAGE
Patients tested	24	
Within + or - 15	23	96
Minus 20	1	4
Less than - 5	6	25

Basal metabolic rate (Table III): None of our patients exhibited frank clinical evidences of thyroid dysfunction such as thyrotoxicosis or myxedema. The prepregnancy basal metabolic rate in all our cases was within the commonly accepted range of + or –15 except one patient in whom the basal metabolic rate, made several times, averaged -20. She presented no distinct clinical features of hypothyroidism and had a normal serum cholesterol, but because of the hypometabolism she was regarded as "hypothyroid." Only six patients had an average basal metabolic rate less than -5.

Rh factor: A test for the Rh factor was made in all of the 24 cases (Table IV). In a majority of the cases the Rh had also been previously taken in this or other hospitals fol-

TABLE IV. STUDIES PRIOR TO PREGNANCY: RH FACTOR

	NO. OF CASES	PERCENTAGE
Rh test on mother	24	
Positive	22	92
Negative*	2	8
Rh test on father	14	
Positive	14	100
Negative	0	0

*Both husbands were Rh positive. Both patients were gravida iii (2 abortions each).

lowing the last abortion. Twenty-two of the patients were found to be Rh positive. Two patients were found to be Rh negative, and their husbands were Rh positive. Rh antibody titers were made at monthly intervals during the pregnancies of these two patients, but no agglutination occurred in a dilution of 1:1. One of these patients had a missed abortion, the other delivered a full-term normal baby. They had each had two previous abortions.

Examination of the endometrium (Table V): The endometrium was examined in eleven patients in the premenstrual phase.

The tissue was obtained by full curettage in two cases and by endometrial biopsy of at least two sites in nine patients. Urine hormone assays were made in the same cycle.

In two of the cases an interval endometrium was found, indicating that in these particular cycles ovulation had not occurred; estrogen and pregnandiol determination were also diminished in these instances. It is probable that in some of these patients with diminished fertility anovulatory cycles are frequent and in two other cases late proliferative changes were obtained with questionable or imperfect secretory function. In both of these cases estrogens and pregnandiol were diminished. In the other seven instances a normal secretory endometrium was obtained. In one instance a marked decidual reaction was noted and this patient was found to have been pregnant at the time the biopsy was taken; fortunately she carried to term.

TABLE V. STUDIES PRIOR TO PREGNANCY: EXAMINATION OF PREMENSTRUAL ENDOMETRIUM

(Biopsy or dilatation and curettage)

	NO.	PERCENTAGE
NUMBER OF CASES	11	
Good secretory function	7	64
Impaired secretory function	2	18
Interval endometrium	2	18

TABLE VI. STUDIES PRIOR TO PREGNANCY: HORMONE ASSAYS

	NO.	PERCENTAGE
Urine Gonadotropins		
(Mid-cycle)	15	
Within normal	13	87
Diminished	1	7
Excessive	1	7
*Urine Estrogens**		
(Mid-cycle & premenstrual)	15	
Within normal	5	33
Diminished	10	67
*Urine Pregnandiol**		
(Premenstrual) (2 assays)	15	
Within normal	7	47
Diminished	8	53

*Eight (53%) of the 15 patients had a combined estrogen and pregnandiol deficiency.

Urine hormone assays prior to pregnancy (Table VI): Urine hormone assays were made in 15 cases. A 24-hour urine specimen collected at the mid-cycle was assayed for gonadotropins and estrogens. A 48-hour specimen collected one week later was assayed for estrogens and pregnandiol. The methods which we employ in our laboratory and the results obtained in normal cases have been published.[11]

The gonadotropins were assayed by the mouse-uterine weight method on an alcohol precipitate of the urine. Estrogens were assayed on spayed mice on a carbon tetrachloride extract of the hydrolyzed urine. Pregnandiol was determined by the gravimetric method of Venning and Browne.[12]

Gonadotropins were found to be within normal (16 to 40 M.U.) in 13, or 87 per cent, of the 15 cases. In one case, in which there was also an interval type of endometrium, the gonadotropins were diminished; and in another associated with a normal secretory endometrium, a high value of more than 96 M.U. was obtained. We have occasionally noted such high values at the mid-cycle.

Urine estrogens were found to be within the normal range (32 to 100 M.U.) at both the mid-cycle and third week in only 5, or 33 per cent, of the 15 cases. Estrogens diminished below this value occurred in 10, or 67 per cent, of the cases; in 4 of these normal values

were noted at the mid-cycle but were low in the second specimen. In 9 of the 10 instances low values were noted during the third week; only one patient had a normal third-week value and diminished mid-cycle value.

Urine pregnandiol determinations were made in 15 cases. Values less than 2 mg. per 24 hours were considered diminished, and were encountered in 8 of the patients. In 3 cases no precipitate at all was recovered. In 4 of these 8 cases the endometrial findings were also abnormal. In 7 patients values of 4 to 12 mg. of pregnandiol per 24 hours were found.

Hormone Assays During Pregnancy.—Serum gonadotropins, serum estrogens, and urine pregnandiol were determined on 19 patients prior to the onset of treatment. In three instances these studies were repeated at monthly intervals during the course of treatment, while the other patients had at least one additional assay made during early pregnancy. The results given below are based on the initial assay made prior to the onset of treatment. It has been our routine to consider values less than 50 per cent of our average normal as diminished.

Serum gonadotropins: Serum was assayed for gonadotropic hormone in infantile mice by determining the least amount necessary to produce corpora hemorrhagica or corpora lutea in two-thirds of the mice and compared to the normal range previously published from our endocrine laboratory. In 18 cases, or 95 per cent, the values fell within the normal range. One patient showed diminished gonadotropins at six weeks, had an episode of spotting several weeks later, but went on to full term.

Free serum estrogen (Fig. 1): Free serum estrogens were determined in whole serum by studying the histologic response of the vagina of the castrate mouse to varying amounts of serum. Results were compared to normal values for the period of gestation as previously obtained in our laboratory. Diminished estrogen values were obtained in 15 of the 19 patients studied. In only 4 instances were the estrogen values considered to be within the normal range. The serum estrogen values made at approximately monthly intervals in three cases are shown in Fig. 1.

Urine pregnandiol (Fig. 2): Sodium pregnandiol glycuronidate was determined by the gravimetric method of Venning and Browne[12] on complete 24-hour urine specimens in 18 cases. Fifteen of these patients showed pregnandiol levels which were diminished to 50 per cent or less of the normal expected value for the period of gestation. The repeat assays on 3 patients are also shown in Fig. 2.

TABLE VII. TREATMENT IN PREVIOUS PREGNANCIES

	NO.	PREGNANCIES SAVED
Patients treated	19	
Pregnancies treated	32	
Progesterone	21	0
Progesterone 20 mg. or more per week	11	
Estrogen and progesterone	1	0*
Thyroid extract	26	0
Vitamin E	20	0

*Successfully treated with estrogen and progesterone in next pregnancy.

Previous Treatment (Table VII).—Nineteen of the 24 patients received prophylactic treatment in the hope of preventing abortion during one or more of their previous pregnancies. In addition to increased amount of bed rest, therapy consisted of administration of thyroid extract, vitamin E, or injections of progesterone. Many of the treated patients received a combination of therapy. Treatment of this kind was administered in at least 32 of the 80 previous pregnancies. In 21 of the pregnancies it is known that progesterone was given biweekly by injection. In only 11 of the cases was the dosage known to be 20 mg. or more per week. None of the patients treated with progesterone in previous pregnancies carried to term. It is of interest that one patient who had had 11 previous pregnancies aborted during the third, fourth, fifth, and sixth pregnancies when she received progesterone but carried to term during the seventh pregnancy in which no treatment was given. In at least 26 of the pregnancies thyroid was administered and in at least 20 of the pregnancies vitamin E was taken.

One patient received progesterone, 10 mg. and estradiol, 10,000 rat units by injection twice a week during her last pregnancy and carried to the twenty-sixth week and miscarried. This patient delivered an almost full-term baby with similar treatment during this pregnancy when injections were continued to the thirty-second week.

Treatment During Present Pregnancy.—In this group of 24 patients treatment was limited to the injection of estrogen and progesterone except in one patient with a basal

metabolic rate of −20, who received 2 grains of thyroid extract daily in addition. Ten milligrams of progesterone and 10,000 rat units of alpha-estradiol benzoate* were given intramuscularly in the same syringe two to three times weekly. Treatment was started by the fourth week of gestation in six cases and by the tenth week in the remainder. Treatment was continued to term in eight cases. In six of these, patients fell into labor while they were still under treatment. One patient had treatment for three weeks only at which time she aborted. Wherever possible, treatment was continued at least to the twentieth week of gestation. The duration of treatment was adjusted as a rule to run beyond the time when the patient generally aborted or miscarried. Patients who had late miscarriages in previous pregnancies were generally given injection three times weekly as they approached the usual time for miscarriage.

No untoward local or general reactions to therapy were observed.

No vitamin E or other vitamin therapy was given except for the usual mixed vitamin capsule containing the minimal daily vitamin requirement which many of these patients were in the habit of taking. None of the patients were confined to bed except during episodes of bleeding, backache, or other symptoms suggestive of possible beginning miscarriage.

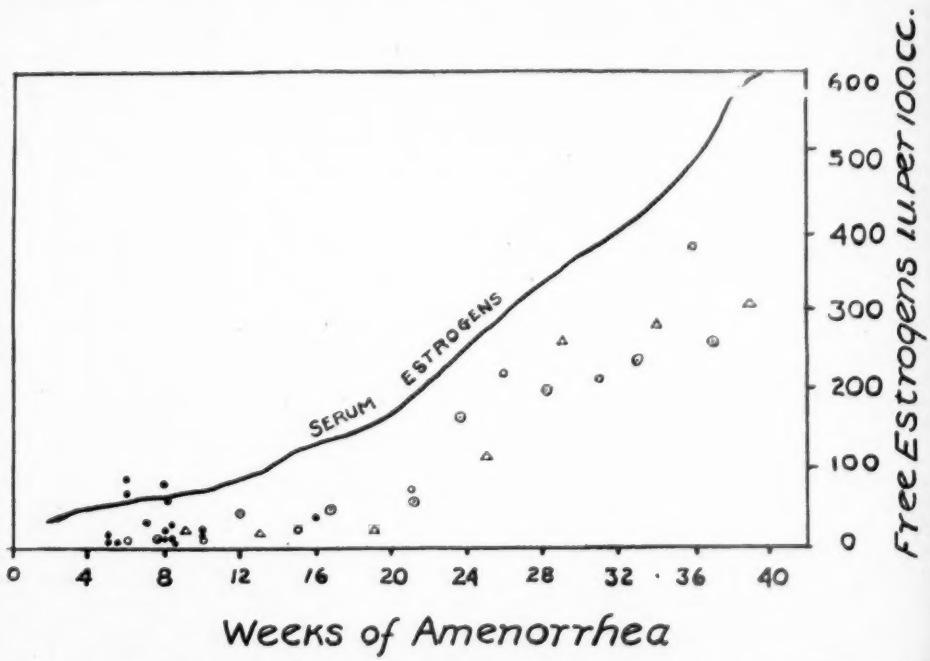

Fig. 1.—Curve showing the average normal serum estrogen values from data accumulated in our laboratory (by the method employed for these assays, 1 M.U. was equal to approximately 5 I.U. of estrone). The solid black dots indicate the serum estrogen values on initial assay in 19 cases studied.

○ indicates the serum estrogen values in A. K., gravida iii, para 0, who was treated with progesterone and estrogen from the seventh week to the twenty-fourth week and delivered a full-term normal baby.

◉ The serum estrogen values in H. I., gravida iii, para 0, who was treated with progesterone and estrogen from the eighth week to term and delivered a normal living baby.

△ Serum estrogen values on S. M., gravida iv, para 0, who was treated from the tenth week to term and delivered a normal living baby.

Results of Treatment (Table VIII)

Fifteen of the 24 patients had full-term live births. All of these patients had spontaneous deliveries without any unusual complications during labor. Of the 15 pregnancies, 14 of the infants were entirely normal and survived. One patient (A.R.) delivered a full-term living infant with multiple congenital abnormalities including an imperforate anus and polycystic kidneys, which died within twenty-four hours. This patient had two previous abortions and one early miscarriage. A number of Rh studies were made during her pregnancy because of conflicting results by different laboratories as to whether she was Rh positive or Rh negative. Blood was sent to Dr. Philip Levine who reported that she was Rh positive but of a rare subtype. Her husband was Rh positive. No antibody titer developed during pregnancy and the baby at term was not jaundiced or erythroblastotic.

*Progesterone (Proluton) and alpha-estradiol benzoate (Progynon B) were generously supplied for many patients by the Schering Corporation.

TABLE VIII. RESULTS OF TREATMENT

	NO.	PERCENTAGE
Total Number of Pregnancies	24	
Full term live births (1 Neonatal death due to congenital abnormalities)	15	62
Premature live births (2 survived)	3	12
Miscarriages	2	8
Abortions	4	17
Total Number of Living Healthy Infants	16	67

Three patients delivered premature living babies at about seven lunar months' gestation. One of these weighed 4 pounds, was distinctly immature, and survived for only a few minutes. The other two premature babies survived and were otherwise normal.

Of the 4 patients who had normal serum estrogens and urine pregnandiol, 3 had normal living babies; the fourth was the patient referred to above (A.R.) whose baby died neonatally because of congenital abnormalities. Since these three patients did not have hormone assays made after the first trimester it is not known whether these patients developed estrogen and progesterone deficiencies later.

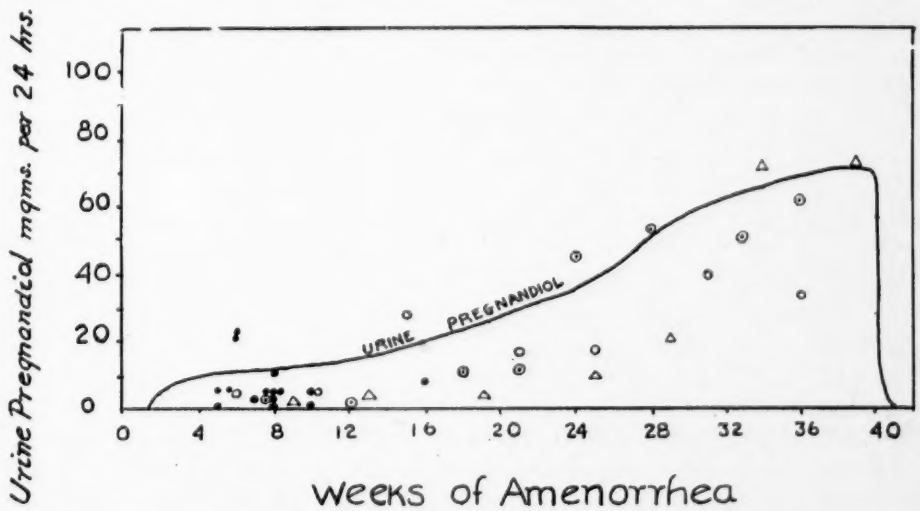

Fig. 2.—Urine pregnandiol values during early pregnancy on 18 patients before start of treatment. Pregnandiol determinations throughout gestation are given for the same three patients indicated in Fig. 1. Curve shows average normal values from data accumulated in our laboratory.

Three patients who had low estrogen and progesterone values on their first assay during the early weeks of gestation, and who were treated with estrogen and progesterone, were followed at approximately monthly intervals by repeat hormone assays (Figs. 1 and 2). It will be noted that despite treatment the hormone values did not return to normal. During late pregnancy there was a tendency for occasional assays of estrogen and progesterone to be within the normal range.

Among the cases which were successfully treated during this pregnancy the following merited special description:

CASE 1.—C. K., aged 24 years. Past medical history and menstrual history entirely normal. Patient married in June, 1940, and became pregnant in October. Miscarried spontaneously in December. By February, 1943, she had had a total of seven spontaneous abortions at approximately eight weeks of gestation in each instance. During six of the pregnancies she received progesterone which in the last two pregnancies was given in a dosage of 20 mg. a week. She also received vitamin E in most of these pregnancies and in three of the pregnancies received thyroid extract despite the fact that the basal metabolic rate was always within normal. Physical examination was entirely negative. Wassermann was negative. The patient and her husband were both Rh positive. Semen analysis was normal. Endometrial biopsy made in the last week of the seventh cycle following her seventh abortion showed a secretory endometrium with a marked decidual reaction. Urine hormone assays made during this week showed pregnandiol, 2 mg. per 24 hours and diminished estrogens (22 M.U.

per 24 hours). When the menses failed to arrive at the expected date, a Friedman test was made one week later and found to be positive. Patient was immediately placed on progesterone, 10 mg. and estradiol, 10,000 rat units, three times weekly, which was continued until the twenty-sixth week and then reduced to twice weekly. The same treatment was continued except that after the twentieth week injections were increased to three times weekly and were continued to the thirty-second week of gestation. Two weeks later she delivered an apparently full-term normal living baby. Hormone assays made at the twentieth and twenty-eighth weeks of gestation showed normal pregnandiol and estrogen titers. Six months following delivery this patient again became pregnant and failed to return to her physician until spotting began at six weeks of gestation. She was again placed on progesterone and estrogen therapy three times weekly and at the present time is five and one-half months pregnant and has felt fetal life.

CASE 2.—M. N., aged 26 years, gravida iv, para 0. Physical examination negative except for moderate obesity. Menses were quite irregular recurring at four- to six-week intervals. Patient was of poor fertility and was treated with thyroid extract and gonadotropic hormone prior to the first pregnancy which terminated in a spontaneous abortion at ten weeks. She became pregnant again two years later after treatment with thyroid and progesterone and received injections of progesterone, 10 mg. weekly until the time of miscarriage at fourteen weeks. Two years later she again became pregnant. Several months before her third pregnancy she showed diminished estrogens and pregnandiol during the last half of the cycle. Her basal metabolic rate was -10. Patient and husband were both Rh positive. A semen analysis was normal. Hormone assays made at the sixth week of gestation showed diminished serum estrogens, diminished urine pregnandiol, and normal serum gonadotropins on two assays. She received injections of progesterone, 10 mg. and estradiol, 10,000 rat units, twice weekly until the twenty-fourth week when she delivered precipitately at home. The baby weighed 4 pounds but lived only for a few minutes. At autopsy it was found to be normal except for prematurity and immaturity. The placenta was grossly and histologically normal. This patient subsequently became pregnant again the following year. Hormone assays made at six weeks of gestation again showed low estrogen assays, made at the twelfth week of gestation continued to show diminished pregnandiol and estrogens but normal gonadotropins. Patient had an episode of bleeding at six and one-half lunar months which stopped in several days and patient was finally delivered at term of a mature normal baby. The placenta was found to be normal on histologic examination.

Unsuccessful Cases.—A total of six babies were lost during pregnancy by abortion or miscarriage; four in the first trimester, two in the second trimester.

CASE 1.—M. G. This patient had two previous abortions. She was first seen for this type of treatment at six weeks of gestation after bleeding had already started and received three injections a week for six weeks. Her basal metabolic rate was -6. Estrogen and progesterone values three months before pregnancy occurred were diminished. No hormone studies were made during pregnancy. She spotted throughout and finally miscarried at twelve weeks. During her second pregnancy she had received progesterone therapy 10 mg. twice a week until time of abortion.

CASE 2.—S. H. Had had one previous stillbirth, cause unknown, and two abortions. Studies made six months before pregnancy showed a normal secretory endometrium and normal estrogen and progesterone excretion during the last half of that cycle; however, hormone assays made at the fifth week of gestation showed normal serum gonadotropins with diminished estrogens and pregnandiol. This patient started treatment at the fifth week, received injections twice a week, and miscarried suddenly without preliminary symptoms at the fourth week. She also received thyroid extract, 1 grain, during this pregnancy.

CASE 3.—H. K., aged 29 years. Had had two previous abortions. She was Rh negative. Her husband was Rh positive. Hormone assays made two months before pregnancy showed normal estrogen and progesterone excretion, but assays repeated at the third week of gestation showed diminished estrogens and pregnandiol and normal gonadotropins. Treatment was started at the third week of gestation and she was given two injections weekly. After the tenth week the uterus failed to enlarge. At the twelfth week the pregnancy test was negative and the patient aborted the following week. No Rh antibody titer developed during this pregnancy. She had received progesterone in her previous pregnancies.

CASE 4.—E. P., aged 22 years, gravida iii. This patient had had two previous abortions. Basal metabolic rate before pregnancy was consistently low (average -20). No hormone studies were made before pregnancy. Assays made at the eighth week of gestation showed

diminished estrogens and pregnandiol and normal serum gonadotropins. Received thyroid extract, 2 grains daily. Injections of estrogen and progesterone started at the eighth week and were given twice weekly. The patient aborted four weeks later.

CASE 5.—E. R., aged 26 years, gravida iii. Had had two previous abortions. Had previously been treated with chorionic gonadotropin to correct menorrhagia believed to be due to a corpus luteum deficiency. Started treatment at the tenth week after bleeding had already started and aborted after three injections. She had been treated with progesterone and vitamin E in her last pregnancy.

CASE 6.—E. S., aged 34 years, gravida iv. First pregnancy resulted in a normal living baby and was then followed by two abortions. Her menstrual history was irregular and she was of poor fertility. Injections twice weekly started at the fourth week. The uterus failed to grow after the eighth week and the contents were expelled at four months. She had received progesterone and vitamin E in her last pregnancy.

There was a total of 18 live births of which 16 survived as living healthy infants making a fetal salvage average of 67 per cent.

Discussion

Endocrine Factors in Habitual Abortion and Miscarriage.—It is generally conceded that the corpus luteum in the human and in certain other species is essential for pregnancy by producing changes in the endometrium favorable to nidation, growth, and development of the fertilized ovum and by inhibiting uterine contractions during the period of implantation and the early weeks of gestation. This is accomplished largely through the action of the corpus luteum hormone, progesterone. It is important to recall, however, that the corpus luteum in addition to making progesterone makes considerable amounts of estrogens. These two hormones are intimately dependent upon each other in producing their physiologic effects. Estrogen is necessary to prime the uterus for the action of progesterone in producing a normal secretory endometrium. On the other hand, progesterone inhibits the excessive destruction of estrogens and facilitates the conversion of estrone to estriol.[13] There is also reason to believe that unless estrogen and progesterone are present in the proper proportions inhibition of uterine contractions will not occur and that, as a matter of fact, a predominance of either hormone may destroy the delicate balance necessary to maintain uterine quiescence.[14]

It is known that in the human the corpus luteum is functionally active only during the early months of gestation. According to results following bilateral oophorectomy during pregnancy, the corpus luteum is generally essential for the normal continuation of gestation during the first trimester. Occasional pregnancies have persisted despite the removal of the ovaries even in the very early weeks of gestation.[15, 16] The functions of the corpus luteum in making progesterone and estrogen are gradually taken over by the chorioplacental system.[8] It is not known with certainty which cells make the estrogens and progesterone but it is believed on indirect evidence[17] that both hormones are made in the syncytial cells of the placenta. During the early weeks of gestation the excretion of estrogen and progesterone in the urine rises but very slowly. It is not until about the eightieth day that the pregnandiol level rises distinctly above the level of 10 mg., its peak in the corpus luteum phase of the normal cycle. Estrogen excretion after this period is also considerably higher than at any time of the normal menstrual cycle. Throughout the remainder of pregnancy the estrogen and progesterone curves roughly parallel each other (Figs. 1 and 2). A few weeks before the onset of labor a large amount of estrogenic hormone which up to this time had been present almost entirely in the conjugated state now becomes freed,[18] indicating important metabolic changes probably preparatory to

the onset of labor. There is also some evidence that shortly before the onset of labor there is a sudden drop in the pregnandiol level.[19]

In reviewing the hormonal physiology of normal pregnancy it is apparent that there are three phases in which deficiencies in estrogen and progesterone may develop: during (a) the immediate postovulatory phase when the corpus luteum may be inadequate because of insufficient pituitary gonadotropic stimulation or abnormalities resident in the ovary; (b) the phase of the corpus luteum of pregnancy, which may be inadequate either because of insufficient chorionic gonadotropic stimulation or local factors in the corpus luteum or ovary; (c) the placental phase, with inadequate production by the placenta after normal or premature failure of the corpus luteum of pregnancy.

Very little is known concerning failure of the corpus luteum immediately following conception. Studies of the endometrium showing poor or "immature" progestational response have been reported[20] but have been held open to question. In our present series there were two such instances of an "early" secretory endometrium. Moreover, more than half of the group of 15 patients studied prior to pregnancy had low urinary estrogens at the mid-cycle and during the third week, with diminished pregnandiol at the latter time. We are, of course, well aware of the dangers of attempting to draw conclusions from isolated hormone assays made on two occasions during one cycle; on the other hand, the findings are quite distinct from those commonly found by us in normal cases. If this syndrome of very early placental failure exists, undoubtedly there are many cases of very early abortion which go unrecognized.

The great majority of pregnancies are spontaneously lost during the first trimester when the bulk of the estrogen and progesterone is being produced by the corpus luteum of pregnancy. It is probable that the enormous amount of chorionic gonadotropin which is being produced at this time is largely responsible for maintaining the function of the corpus luteum. It would seem that deficiency of chorionic gonadotropin is not a frequent cause of corpus luteum failure since it was below the normal range in only one of 19 cases tested in our series. It is only when death of the fetus has been suspected that the chorionic gonadotropins begin to drop and do so quite precipitously. In our experience when the serum gonadotropins have fallen to less than 100 M.U. per 100 c.c. of serum, the fetus is usually nonviable.[21] Administration of chorionic gonadotropin would therefore not be rational therapy as a rule; furthermore, the amounts required in terms of the quantity being produced in early pregnancy would be quite enormous.

The interpretation of diminished pregnandiol determinations in habitual aborters has been made difficult by the observation of diminished values in normal pregnancies.[6, 9] We have also had the experience mentioned by others of a normal live birth following periods when very little or no pregnandiol was excreted on repeated examinations.

In our experience, serum estrogen values are much less subject to the marked day-to-day fluctuation which may be encountered in urinary estrogen values during pregnancy,[22, 23] probably because the estrogens in the blood of pregnancy are largely present in a free state[24] and are not subject to the metabolic changes which occur in the kidney. In our experience a low serum estrogen value coupled with a low urine pregnandiol is of considerably more significance than the latter alone.

The rationale for the addition of estrogens to progesterone may be outlined as follows:

1. Progesterone and estrogen are believed to come from the same sources throughout gestation, and their concentration throughout gestation roughly parallel each other.

2. It is logical to assume that a deficiency in progesterone would be accompanied by a deficiency in estrogen.

3. In our experience such double deficiencies of estrogen and progesterone frequently occur in abortion patients, often appearing early in the gestation and persisting in many cases throughout the period of gestation.

4. There are good reasons to believe that estrogen and progesterone influence the normal reactions of each other upon the uterus and are involved in the normal metabolism of each other.

The early objections to the use of estrogen in abortion patients were chiefly on the basis that estrogens tend to increase the tonus and irritability of the uterus and to favor pelvic congestion. These statements can no longer be accepted as a generalization. Indeed the administration of estrogens in large dosages throughout a large part of pregnancy has been given with impunity to many patients for the treatment of diabetes complicating pregnancy.[25] On the other hand, estrogen in large dosage given to patients with missed abortion and intrauterine fetal death is known frequently to start uterine contractions. We have not been able to bring ourselves to believe that the use of estrogens alone in patients who are threatening to abort is physiologically sound or rationally indicated.

Endocrine Therapy.—There are many reports of a high percentage of successful results following the use of progesterone alone in the treatment of threatened or recurrent abortion. On the other hand, there have been an increasing number of studies in the past several years which have raised serious doubts as to the efficacy of progesterone as compared to similar groups which have not received endocrine therapy.[26-28] Some clinicians have even expressed the opinion that in threatened abortion the administration of progesterone sometimes seems to precipitate expulsion of the products of gestation. Hamblen[6] has suggested that progesterone administration may be undesirable because of possible inhibition of normal progesterone production and metabolism since he has noted that the excretion of pregnandiol was not increased, and occasionally even diminished, following progesterone therapy.

Our own results with progesterone alone, even in dosages of 40 mg. per week, have not been very encouraging. Many of our failures with progesterone therapy are represented in the previous pregnancies of some of the patients represented in this study. The poor results of progesterone therapy in this group cannot, of course, be considered representative of our general experience with progesterone since these cases were selected for further treatment because they were habitual aborters. There were, however, a number of patients in this group whom we had treated repeatedly in previous pregnancies with large dosages of progesterone without success in any instance.

If the administration of estrogen and progesterone in the dosage which we have employed constitutes complete replacement therapy, it might be expected that during the course of therapy the urine pregnandiol levels and serum estrogen would return to normal. Our observations on this point are rather disappointing. In three cases in which we have made observations at monthly intervals, normal levels did not occur until late in gestation when the effects of

administered hormone would have comparatively less influence on the high estrogen-progesterone levels. These observations raise the questions as to whether the dosage we employ is sufficient, whether the mode of administration is the best, and whether these patients may not have some abnormality of estrogen-progesterone metabolism. The last possibility deserves particular consideration in view of the fact that some of our patients exhibited low progesterone and estrogen levels in both the corpus luteum and placental phases.

Summary

1. A study was made of a group of 24 patients with habitual abortion who were treated with estrogen and progesterone.

2. These patients had gone through a total of 80 previous pregnancies from which there had resulted only 7 living babies (9 per cent). There had been 52 abortions, 18 miscarriages, 2 stillbirths, and one premature live birth in which the infant did not survive.

3. Fifty-four per cent of this group had no difficulty in becoming pregnant, 8 per cent were of diminished fertility, and 38 per cent were of poor fertility.

4. In none of these patients were there any pelvic abnormalities or systemic diseases which would influence abortion.

5. In only one patient was the basal metabolic rate diminished.

6. Two patients had Rh incompatibilities (Rh-negative wife and Rh-positive husband). One of these delivered a normal living baby and the others aborted; in neither case did Rh antibodies develop.

7. Examination of the endometrium obtained by biopsy or curettage was available in 11 cases before the present pregnancy. Good secretory function was noted in 7 cases, impaired secretory function in 2, and an interval endometrium in two.

8. Urine hormone assays were made in 15 cases prior to the onset of pregnancy. Urine gonadotropin assays made at the mid-cycle were normal in 87 per cent. Urine estrogens made at the mid-cycle and during the third week of the cycle were diminished in 67 per cent, while low or absent pregnandiol values were obtained in 53 per cent. Since these studies were made in only one cycle, their significance is limited.

9. Hormone assays consisting of urine pregnandiol determinations, serum estrogens, and serum gonadotropins were made early in pregnancy in 19 cases. In almost all of the cases one or more additional assays were made and in 3 cases monthly assays were done.

On the initial assay 95 per cent of the cases showed normal serum gonadotropins. Seventy-nine per cent had diminished serum estrogens and 83 per cent had diminished pregnandiol titers. In 13 of the 19 cases studied, both estrogen and pregnandiol were diminished. These findings indicate a deficiency of the corpus luteum during the early weeks of gestation and an inadequacy of the placenta to take over its functions.

10. Many of these patients had been unsuccessfully treated in previous pregnancies with progesterone, thyroid, and vitamin E.

11. During the present pregnancy all patients were treated by the injection of progesterone, 10 mg., and alpha-estradiol benzoate, 10,000 rat units, given together two or three times weekly. This treatment was generally continued to the period of viability or later.

12. There was fetal salvage of 16 babies, or 67 per cent. There were 15 full-term live births (with one neonatal death due to congenital abnormalities), 3 premature live births of which 2 survived, 2 miscarriages, and 4 abortions.

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Discussion

DR. SAMUEL A. WOLFE.—Dr. Vaux has proved chemically by hormonal assays the functional insufficiency of the corpus luteum of pregnancy as a cause of abortion. Yet for successful pregnancy that is only one of several factors. Additionally, a normally fertilized ovum, a normal embryo, as also a normal uterine decidua are essential. Systemic disturbances, such as the Rh factor, thyroid disorders, diabetes, etc., were of no great moment in the series presented.

We know little about the normal ovum or its fertilization. Whether fertilization by a deformed spermatozoon is a factor in eventual fetal malformation is only presumption. Certain it is that of all abortions occurring in the first month of pregnancy, only 25 per cent are normal. As pregnancy progresses, this incidence falls so that in the second month 50 per cent of embryos are normal. Certainly, a basically deformed embryo is not to be retained by any therapeutic agent. Molar disease of the trophoblast and early hydramnion are little understood. Fleshy moles and hematoma mole are further types of blighted ova which certainly cannot be affected by hormonal therapy.

The uterine endometrium, too, may not always prove a fertile field for implantation of the fertilized ovum. Mixed endometrial patterns occur and focal premenstrual changes (i.e., corpus luteum changes) have been seen in glandular cystic hyperplasia. Whether such uteri afford proper nidation and allow normal development of the fertilized ovum is entirely speculative. It would seem that hormone therapy could hardly help an organ which shows absence of normal response even in the nonpregnant state.

A normally functioning corpus luteum of pregnancy is a third requisite to maintain pregnancy in situ. Its deficiency has been proved by Dr. Vaux's work and the rational of the combined use of estrogen and progesterone rests on a sound basis. Since trophoblast is a normal pituitary stimulant this fetal element may indirectly be involved in the inadequate function of the corpus luteum. The combination of chemical studies in conjunction with examinations of the discharged products of conception would prove a more conclusive method by which to evaluate the effects of therapy. It must be noted that Falls attained excellent results in threatened abortions with a lutein extract free from progesterone. Karnaky using estrone by injection into the cervix also claims excellent therapeutic response to this agent. Shute and Miller-Vogt used vitamin E in threatened abortions, supposedly with excellent results. It would seem, therefore, that in many cases of abortion the results may be good not because of treatment but in spite of the therapy employed. Nevertheless, this paper has established the use of hormone therapy in habitual abortion not upon empiricism but upon a biologic basis.

DR. VAUX (closing).—The glycogen content of the endometrium has been referred to by Dr. Wolfe. That definitely has a very important part in this study. Complete studies of the endometrium and similar studies which we feel might lead us along a more trustworthy path have proved in our laboratory to be of great interest and very helpful in our investigation of habitual abortion.

There is a question as to what is an abnormal ovum. To begin with, we know that we cannot observe or control this finding. However, in the series of cases presented, we did everything possible in the laboratory and in this study to have very close association and coordination between the laboratory and the clinician. The Chief of our Endocrine Laboratory has been most helpful, doing most of the work, with regard to keeping the balance between the normal and the abnormal as far as the endocrinological side of this subject is concerned. We have felt that that was a very important part of the question of treating habitual abortion cases. We have found in many years of study, including laboratory investigations, that there was a great discrepancy in these two, the laboratory and the clinical side. When a balance was maintained we were at least 67 per cent better than previously when balance was ignored.

Corpus luteum failure is undoubtedly the basis of the deficiency in the progesterone and estrogen determinations. In pregnancy the levels were irregular and untrustworthy in a number of these patients when made previous to pregnancy and during the course of pregnancy.

The other important subject, I believe, is the cooperation of the patient. We were fortunate in having 24 of these women, who, as I pointed out, had 80 pregnancies and only 7 live births. They were treated very irregularly in their previous pregnancies and got tired of it and did not continue the treatment. We selected these women in the hope that we could throw a little further light on this rather interesting and very important topic of why so many of the patients we see in the clinic as well as in private practice habitually abort. We only hope we have added something of value and that future studies and discussions, as pointed out, may bring us to a very much happier conclusion.

RENAL GLOMERULAR AND TUBULAR FUNCTION IN RELATION TO THE HYPERURICEMIA OF PRE-ECLAMPSIA AND ECLAMPSIA

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PERHAPS the most outstanding change in the blood chemistry in eclampsia and pre-eclampsia is in the uric acid, which usually increases. Stander and Cadden,[1] from a study of 148 cases, concluded that the blood uric acid "... gives us an accurate index of the severity of pre-eclampsia and the extent of liver damage, if present ... and thus is our best criterion for any given type of treatment." As is implied in the quotation, these workers considered that hyperuricemia points to impairment of liver function.

The factors which, if uncompensated, would make for hyperuricemia are:

1. Increased production of uric acid in the body.
2. Decreased renal excretion.
3. Decreased destruction of uric acid in the body.

The question as to increased production of uric acid in pre-eclampsia remains unanswered, and almost unasked. As for the second factor, Cadden and Stander[2] reported normal excretion in five cases of eclampsia. By "normal excretion" they meant that the eclamptics, on a purine-free diet, excreted from 130 to 740 mg. of uric acid per twenty-four hours. This they compared with the 300 to 500 mg. excretion which Burian and Schur[3] found in normal individuals. As we shall show in the discussion below, these data of Cadden and Stander may be reinterpreted.

Schaffer, Dill, and Cadden[4] have measured simultaneously the clearances of diodrast, inulin, urea, and uric acid in normally pregnant and in pre-eclamptic women. They found that in pre-eclampsia the uric acid clearance averaged 31 per cent less than in their normals. They attributed the diminished uric acid clearance to a decrease in glomerular filtration (which showed a reduction of 20 per cent). Their data are open to the objection that they measured their clearances in the presence of plasma diodrast concentrations of the order of 1 to 2 mg. per 100 ml. Such plasma levels of diodrast will increase the uric acid clearance two- to threefold.[5, 6] It is uncertain whether diodrast would have quantitatively the same effect upon the pre-eclamptic kidney as upon the normal. Furthermore, detailed study of their data for individual cases leaves one unconvinced that a reduction in the filtration rate is chiefly responsible for the decreased uric acid clearances. Recalculation of their data shows a more general factor—in pre-eclampsia there seems to be an increased tubular reabsorption of filtered uric acid. (Uric acid is filterable from human plasma.[7])

In the present paper we are reporting the measurements of simultaneous clearances of inulin, urea, and of uric acid as determined by two methods. Inulin does not affect the uric acid clearance.[5]

Material and Methods

Antepartum clearances were measured in ten normally pregnant women near term. In eight of these, the clearances were repeated six to twelve days postpartum. Similar clearance determinations were made antepartum and repeated postpartum in eight cases of pre-eclampsia and two cases of eclampsia. No patient was in labor at the time of the test al-

though some delivered within twenty-four hours. (Crawford[8] has found that the blood uric acid rises considerably during labor, perhaps because of retarded renal excretion.)

The night before the test, the patient was given a liter of water to drink. Beginning at 5:30 the morning of the test, she was given 200 ml. of water every half hour until the test was started (usually between 7 and 9 A.M.). The fasting patient was catheterized, a blank blood sample obtained, and an infusion set up. The infusion consisted of 700 ml. of 5 per cent dextrose containing 7 Gm. of inulin, and was given at the rate of 4 ml. per minute. Once the infusion was begun, 3 Gm. of inulin (in 10 per cent solution) were injected through the rubber tubing. At least half an hour later, the bladder was emptied, and a blood sample taken. Three urine samples were then obtained, usually at twenty-minute intervals unless the urine volume were low, in which case the collection periods were prolonged to as much as an hour. Further blood samples were taken midway in the second and again at the end of the third urine collection periods. At each emptying of the bladder, 50 c.c. of air repeatedly were blown into the bladder and suprapubic pressure used to force out the residual urine.

All clearances were calculated as $\frac{UV}{S}$, where UV is the quantity in milligrams of inulin, urea, or uric acid excreted per minute, and S is the concentration of the substance in the serum, in milligrams per milliliter. The data given in the tables are the averages of three clearance periods. Urine volumes were usually either decreasing or nearly constant.

Serum filtrates were made by the method of Somogyi[9] for the inulin analyses. For urea and uric acid determinations, 3 ml. of serum were added to 13.5 ml. of distilled water; to this were added 1.5 ml. of 10 per cent sodium tungstate and, slowly with shaking, 12 ml. of N/12 sulfuric acid.

Inulin was determined in serum filtrates and in diluted urine by the fructose method of Roe,[10] as suggested by Hubbard and Loomis.[11] Serum and urine analyses were done simultaneously and with a set of 5 standards (2.5 to 4.5 mg. per 100 ml.). This is important, because the color development is very sensitive to small changes in temperature, and the factor k_1 therefore varies. Readings were made with an Evelyn photoelectric colorimeter. Blood sugars were determined, since high concentrations of dextrose give some color in the inulin measurement.

Urea in serum filtrates and urine was determined by the manometric urease methods of Van Slyke.[12]

Uric acid in serum filtrates and in diluted urine was determined by (a) Folin's direct method,[13] and (b) a modification of the photoelectric method described in the manual of the Rubicon Company.[14] In this modification, the blanks were prepared by removing uric acid from serum filtrates and urines by treating with Lloyd's reagent. Folin[13] writes that this treatment removes "all of the uric acid, nearly all of the creatinine, and very little else." The uric acid-free urines were then diluted to the same degree as were the samples for analysis.

All determinations, except urine urea, were done in duplicate.

Results

Tables I and II summarize the data for ten normal subjects. The individual clearances have not been corrected to the conventional surface area of 1.73 square meters. The averages, standard deviations, and ranges have been calculated from clearances so corrected. In estimating the surface area, the prepregnancy weights have been used. (Nearly, if not quite all studies of clearances in pregnancy have been corrected from the patients' actual weights, if corrected at all. Since the average patient near term weighs 20 to 30 pounds more than she did before pregnancy, or will weigh in a week or two after delivery, this makes an appreciable difference. We chose the prepregnancy weight because there is no evidence that the kidneys increase in size and functional capacity during pregnancy and recede rapidly in the puerperium. The usual correction for surface area is, of course, based upon the observation that renal size and clearances roughly parallel the body surface area. The uncorrected clearances are presented in the tables in order that the antepartum and postpartum values may be compared.)

There is no significant difference between the antepartum and postpartum averages. The average inulin and urea clearances of 128 and 78 ml. per minute, respectively, are about 10 per cent higher than the averages generally reported for women. The uric acid clearances as determined by the two methods check very closely, and are in the middle of the range reported for normal nonpregnant adults.

TABLE I. DATA FOR NORMAL PATIENTS, ANTE PARTUM
(Individual clearances not corrected for surface area)

NO.	AGE	GRAVIDA	WEEKS PREGNANT	SURFACE AREA IN SQ.M., FROM PREPREGNANT WEIGHT	SURFACE AREA IN SQ.M., FROM ACTUAL WEIGHT DAY OF TEST	SERUM URIC ACID, MG. PER 100 ML.	AVERAGE URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN. INULIN	UREA	URIC ACID FOLIN	URIC ACID PHOTEL.
1	31	viii	42	1.57	1.81	4.87	7.84	129	81	13.4	14.0
2	20	ii	39	1.51	1.59	3.39	2.00	159	113	22.7	22.8
3	22	i	38	1.56	1.73	4.67	2.50	125	54	12.6	12.7
4	26	v	37	1.59	1.66	3.47	0.69	90	43	14.0	13.5
5	42	x	41	1.74	1.76	3.86	1.70	171	101	16.6	14.5
6	19	i	38	1.65	1.71	4.31	6.91	129	93	15.1	14.9
7	24	iv	40	1.63	1.71	3.92	4.14	127	53	16.8	16.8
8	33	vii	36	1.84	1.89	3.06	3.43	82	40	10.5	10.2
9	22	iii	35	1.64	1.68	3.21	2.76	143	101	17.0	15.9
10	23	iv	32	1.69	1.82	2.92	1.35	92	–	17.2	16.3
Averages				1.65	1.74	3.77	3.33	125	75	15.6	15.1
Clearances per 1.73 square meters body surface area, corrected from prepregnancy weights					Averages			131	79	16.3	15.8
					Standard deviations			32	29	3.9	3.9
					Ranges			77 to 182	38 to 130	9.9 to 26.0	9.6 to 26.1

TABLE II. DATA FOR NORMAL PATIENTS, POST PARTUM
(Individual clearances are not corrected for surface area)

NO.	ANTE PARTUM DAYS (A.P.)	ANTE PARTUM URIC ACID/INULIN CLEARANCE RATIO FOLIN	ANTE PARTUM URIC ACID/INULIN CLEARANCE RATIO PHOTEL.	POST PARTUM DAYS (P.P.)	SERUM URIC ACID MG./100	AVERAGE URINE VOLUME ML./MIN.	CLEARANCES IN ML. PER MIN. INULIN	UREA	URIC ACID FOLIN	URIC ACID PHOTEL.	URIC ACID/INULIN CLEARANCE RATIO FOLIN	URIC ACID/INULIN CLEARANCE RATIO PHOTEL.
1	12	0.104	0.109	9	5.84	10.69	125	80	16.8	17.9	0.134	0.143
2	6	0.143	0.143	6	3.77	7.58	110	80	16.6	16.2	0.150	0.147
3	2	0.101	0.102	9	3.88	6.81	135	89	21.2	20.3	0.156	0.150
4	2	0.156	0.150	7	3.84	4.78	126	79	13.7	14.0	0.109	0.111
5	11	0.098	0.085	7	4.64	4.75	134	79	12.3	12.8	0.092	0.096
6	15	0.117	0.115	12	4.75	5.77	111	57	8.2	8.0	0.074	0.072
7	17	0.132	0.132	6	5.10	8.84	100	60	11.4	11.5	0.113	0.115
8	13	0.128	0.124	8	4.96	5.19	105	55	11.2	11.0	0.107	0.105
9	1	0.119	0.111									
10	22	0.187	0.177									
Averages		0.128	0.125	8	4.60	6.80	118	72	13.9	14.0	0.117	0.119
Clearances per 1.73 square meters body surface area, corrected from prepregnancy weights				Averages			126	77	14.9	14.9		
				Standard deviations			16	16	4.7	4.6		
				Ranges			99 to 150	52 to 99	8.6 to 23.5	8.4 to 22.5		

Table III summarizes the rather meager literature on the normal uric acid clearance. Neither of the two papers dealing with uric acid clearances in pregnancy can be accepted as giving reliable values. Schaffer, Dill, and Cadden[4] determined their clearances in the presence of diodrast; Nayar[21] studied Indian women, whose average normals in many respects are far from anything seen in normal occidental women. Moreover, Nayar assumed that the rate of uric acid excretion has an augmentation limit at a urine volume of 2 ml. per minute, and arbitrarily used the square root of the volume in calculating his clearances. What he reports as "clearances" are therefore too low whenever the urine volume fell between 1 and 2 ml. per minute, since Brøchner-Mortensen[19] found the augmentation limit to lie between 0.5 and 1 ml. per minute.

The clearance ratio of uric acid/inulin is of special interest. This ratio gives the proportion of filtered uric acid which is finally excreted in the urine. The lower the ratio, the greater has been the renal tubular reabsorption of filtered uric acid. In the ten normal cases, this ratio averages about 12.2 per cent (12.8 per cent ante partum and 11.7 per cent post partum). The lowest antepartum ratio is 9.8 per cent. There is no consistent direction of change with delivery; in 3 cases the ratio increased, in 5 it decreased, and in 2 no postpartum observations were made.

TABLE III. A REVIEW OF THE LITERATURE ON URIC ACID CLEARANCE IN NORMAL ADULTS
("Original formula" rephrased for uniformity. UV = minute excretion in milligrams. B, P, or S = blood, plasma, or serum concentration in milligrams per milliliter)

AUTHOR	YEAR	CASES	URIC ACID METHOD	URIC ACID CLEARANCE ML. PER MINUTE	CLEARANCE RATIO $\frac{\text{URIC ACID}}{\text{INULIN}} \times 100$	ORIGINAL FORMULA
Watanabe[15]	1917	5	Folin and Denis Benedict and Hitchcock	Whole blood 8.9	-	$\frac{B}{UV \times 60}$
Steinitz[16]	1922	?	Hopkins-Morner	Whole blood 11.7	-	$\frac{B}{\sqrt{1.44\ UV}}$
Berglund and Frisk[17]	1935	76	Folin (1933)	Unlaked blood 19.0	-	$\frac{60\ UV}{B}$
Gärdstam[18]	1935	20	Folin (1922)	Plasma 13.5*	-	$\frac{UV}{P}$
Brøchner-Mortensen[19]	1940	16	Own (Ferricyanide reduction	Plasma 6.9	-	$\frac{UV}{P}$
Coombs and associates[20]	1940	8	Benedict and Behre	Plasma 11.1	9.8	$\frac{UV}{P}$
Nayar[21]	1940	43	?	Whole blood (7.7)†	-	$\frac{U\sqrt{V}}{B}$
Schaffer, Dill and Cadden[4]	1943	12	Folin (1933)	Plasma (31.9)†	(30.3)†	$\frac{UV}{P}$
Bonsnes, Dill and Dana[6]	1944	20	Folin (1922)	Plasma 14.6	-	$\frac{UV}{P}$
Present study	1945	10	Folin (1933) Photoelectric	Serum 15.7	12.2	$\frac{UV}{S}$
Totals and Mean		165‡		15.3		

*Averages of 8 to 9 and 9 to 10 a. m. periods. Bonsnes calculated an average of 12.9 for the first periods, Brøchner-Mortensen got an average of 11.9 for all periods.

†Not averaged. Nayar's formula does not give true clearances, and Schaffer and associates used diodrast.

‡Steinitz arbitrarily credited with ten cases.

TABLE IV. TOXEMIA PATIENTS, ANTE PARTUM
(Recorded observations refer to the day of the test)

NO.	AGE	GRAVIDA	WEEKS PREGNANT	SURFACE AREA IN SQ. M., FROM PREPREGNANT WEIGHT	SURFACE AREA IN SQ. M., FROM ACTUAL WEIGHT	BLOOD PRESSURE SYSTOLIC/DIASTOLIC MM. HG	PROTEINURIA GRAMS PER LITER	EDEMA
Pre-eclampsia								
11	23	vi	38	1.69	1.76	190/110	12	2 plus
12	26	i	41	1.49	1.59	158/102	12	3 plus
13	18	i	41	1.68	1.84	138/110	v. f. tr.*	2 plus
14	28	i	36	1.54	1.57	138/ 98	2	2 plus
15	43	v	41	1.89	1.87	142/ 92	v. f. tr.*	1 plus
16	31	iii	28	1.52	1.58	138/ 90	v. f. tr.*	1 plus
17	30	vi	30	1.73	1.89	160/100	10	3 plus
18	38	iii	34	1.58	1.67	160/114	34	3 plus
Eclampsia								
19	21	i	32	1.57	1.68	140/ 70	3	2 plus
20	18	i	38	1.59	1.82	160/110	30	3 plus

*v. f. tr. = very faint trace; slight turbidity on addition of sulfosalicylic acid.

Table IV describes the status of the pre-eclamptic and eclamptic patients, as of the day of the test. All had been hospitalized for some days before the tests were done; for this reason the recorded blood pressures, proteinuria, and degrees of edema often represent improvement over the status on admission. As for the 2 eclamptic patients, Case 19 was done

six days after a series of convulsions and intrauterine death of the fetus; Case 20 was done fifteen hours before the first of a dozen fits. All cases were known to have had normal blood pressures in pregnancy, until the onset of toxemia.

The antepartum clearance observations in the pre-eclamptic and eclamptic patients, which are summarized in Table V, show considerable reductions from the average normal. Thus, the inulin clearance averages 25 per cent below the average normal. Our average urea clearance is reduced in exactly the same degree, and thus the urea/inulin clearance ratio remains at the usual figure of 0.60. The uric acid clearance is decreased in considerably greater degree, and averages only 50 per cent of the normal mean. Cases 12 and 20 are not included in the averages, because the marked oliguria makes for probable collection errors. Of the eight cases with satisfactory urine outputs, only two had inulin clearances below the normal range (Cases 11 and 18). On the other hand, all but three did have uric acid clearances falling below the range of the normal series.

TABLE V. CLEARANCES IN PRE-ECLAMPSIA AND ECLAMPSIA, ANTE PARTUM

(Cases 12 and 20 not averaged because of oliguria)

NO.	SERUM URIC ACID, MG. PER 100 ML.	MEAN URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN.				URIC ACID/INULIN CLEARANCE RATIOS		DAYS BEFORE DELIVERY
			INULIN	UREA	URIC ACID FOLIN	URIC ACID PHOTEL.	FOLIN	PHOTEL.	
Pre-eclampsia									
11	8.50	1.61	63	–	5.4	5.5	0.086	0.087	1
12	8.49	0.13	17	–	1.1	1.2	0.064	0.071	1
13	6.47	2.48	115	63	10.5	10.5	0.092	0.092	3
14	5.71	2.51	100	41	6.9	7.6	0.069	0.076	9
15	6.35	2.35	99	55	9.1	8.8	0.092	0.089	6
16	4.72	4.72	94	54	7.3	6.9	0.078	0.073	30
17	6.46	1.56	103	–	5.3	5.6	0.051	0.054	5
18	6.18	1.53	62	–	6.2	6.8	0.100	0.110	7
Eclampsia									
19	8.45	5.23	105	67	8.4	8.3	0.080	0.079	8
20	6.17	0.30	40	–	3.6	3.5	0.090	0.088	1
Means	6.61	2.75	93	56	7.4	7.5	0.081	0.081	8
Clearances per 1.73 square meters of body surface area, corrected from prepregnancy weight	Means		98	59	7.7	7.9			
	Standard deviations		20	10	1.7	1.7			
	Ranges		65 to 118	46 to 74	5.3 to 10.8	5.6 to 10.8			

TABLE VI. CLEARANCES IN PRE-ECLAMPSIA AND ECLAMPSIA, POST PARTUM

NO.	SERUM URIC ACID, MG. PER 100 ML.	MEAN URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN.				URIC ACID/INULIN CLEARANCE RATIOS		DAYS AFTER DELIVERY
			INULIN	UREA	URIC ACID FOLIN	URIC ACID PHOTEL.	FOLIN	PHOTEL.	
11	6.29	7.55	103	63	8.3	8.2	0.080	0.079	9
	4.32	5.75	148	93	19.8	21.4	0.134	0.145	6 months
12	3.22	7.64	108	70	22.2	20.5	0.206	0.190	10
13	4.84	5.40	100	66	13.0	14.2	0.130	0.142	8
14	4.21	5.58	80	–	11.3	13.4	0.142	0.168	7
15	5.88	3.95	113	78	10.7	10.2	0.095	0.090	6
	4.24	10.20	117	76	11.6	13.7	0.100	0.117	7 weeks
16	4.42	5.06	94	56	10.0	10.8	0.107	0.115	6
17	4.51	6.05	137	98	15.3	17.0	0.112	0.124	7
18	3.40	3.28	119	80	16.7	16.8	0.140	0.141	6
19	5.45	6.03	103	82	9.9	10.0	0.098	0.098	6
20	4.51	1.47	101	–	15.8	17.0	0.156	0.168	9
Means*	4.31	5.65	110	78	14.6	15.5	0.133	0.141	
Clearances per 1.73 square meters of body surface area, corrected from prepregnancy weight	Means		117	82	15.6	16.4			
	Standard deviation		18	12	3.6	4.4			
	Ranges		90 to 151	64 to 98	9.8 to 25.8	9.3 to 23.8			

*In cases 11 and 15, only the second clearances are included in the averages.

The clearance ratio of uric acid/inulin is reduced by about one-third. *With one exception, the highest ratio in the ten pre-eclamptics is lower than the lowest ratio in the ten normals* (Fig. 1). This lowered clearance ratio points to an increased tubular reabsorption of uric acid in pre-eclampsia and eclampsia. This is the factor most generally operative in reducing the uric acid clearance.

The postpartum clearances in the pre-eclamptics and eclamptics show a return to normal (Table VI). Schaffer, Dill, and Cadden[4] similarly found a rapid return to normal in the four pre-eclamptics whom they checked post partum, although part of the apparent increase is attributable to their corrections on the basis of weights at the time of the tests.

More significantly, the clearance ratio of uric acid/inulin also returns to normal after delivery. This ratio increased post partum in every case. As Fig. 1 shows, the ratio jumped from the low antepartum values up into the normal range in all but one case. In Cases 11 and 15, the ratios had not attained a normal level within the first week post partum. Repetition of the tests at six months and seven weeks, respectively, gave normal ratios.

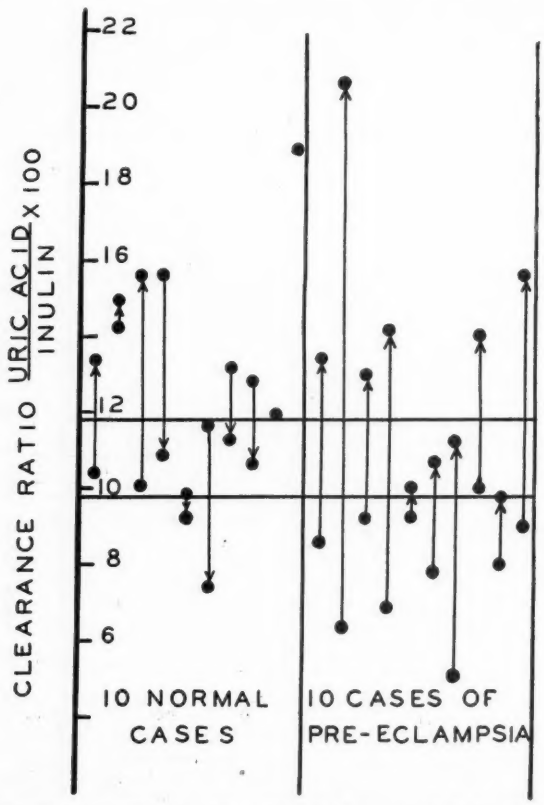

Fig. 1.—The fraction of filtered uric acid finally excreted in the urine. The arrow denotes the direction of change with delivery. (Clearance ratio = fraction excreted.) Upper line = average normal antepartum clearance ratio. Lower line = lowest normal antepartum clearance ratio. Note that the highest antepartum ratio in pre-eclampsia is lower than the lowest antepartum ratio in the normal series (one exception). Note also that every pre-eclamptic shows a rise in the ratio, with delivery, while there is no consistent direction of change in the normal series.

Discussion

Stander and Cadden,[1] in 1934, stated: "As yet we are not in a position to state that the excretion of uric acid is decreased in eclampsia. There is, however, sufficient evidence to make us believe that the accumulation of uric acid in the blood in eclampsia is not the result of decreased kidney function, but rather the result of a metabolic change. This metabolic change seems to be dependent upon liver damage." In 1939,[2] they concluded that the renal excretion of uric acid is normal in eclampsia (see above), and that the hyperuricemia therefore depended upon liver impairment.

The physiologic measure of the kidney's efficiency, however, is not merely the quantity of uric acid excreted in unit time. Rather, the true measure is the *clearance*. A clearance is calculated by dividing the quantity of substance excreted in unit time by the concentration of the same substance in the plasma. Thus a kidney of 50 per cent efficiency (clearance half of normal) will excrete the same quantity of uric acid in unit time as will the kidney of 100 per cent efficiency, provided that the plasma concentration of uric acid be doubled in the patient with the 50 per cent clearance. The five patients with eclampsia, studied by Cadden and Stander,[2] all had hyperuricemia. Dividing the "normal excretion" by the increased plasma concentrations would, then, give subnormal clearances. The rough calculations possible from their data indicate that all five of these patients had uric acid clearances of less than 50 per cent of average normal. A renal factor does, then, appear to be operative in the retention of uric acid in eclampsia.

As has already been mentioned, Schaffer, Dill, and Cadden[4] found the uric acid clearance to be decreased by an average of 31 per cent in their pre-eclamptics. Our own data show an average reduction of 50 per cent in the uric acid clearance. The average serum uric acid in these toxemias was increased 75 per cent over the mean level in the normal series. The diminution in the clearance seems great enough to account for the rise in serum levels. If we assume a constant production and destruction (if any) of uric acid in these patients, then a 50 per cent reduction in the renal clearance might be expected to cause a rise, up to double the initial serum concentration. In several of our pre-eclamptic patients we predicted rises in the blood uric acid on finding low clearances. Thus, in Case 16, the whole blood uric acid was 3.5 mg. per 100 ml. on the day of the clearance test. The uric acid clearance was half of average normal. Two weeks later, the whole blood uric acid had climbed to 5.4 mg. per 100 milliliters.

From the above considerations, we see no need for invoking liver impairment as a causative factor in the hyperuricemia of pre-eclampsia and eclampsia. Our study has no immediate bearing upon the rest of the quotation from Stander and Cadden,[1] that the blood uric acid ". . . gives us an accurate index of the severity of pre-eclampsia. . . ." Whatever may have been established in this connection still stands; we question only that the hyperuricemia means liver damage. If an increased blood uric acid does point to severe pre-eclampsia, how are we to interpret a lowered uric acid clearance which will lead to a rise in the blood level? Is the clearance an earlier measure of severe toxemia?

In the averages, the diminution in the uric acid clearance is attributable to two factors exactly equal in effect. The factors are (a) reduction in the rate of glomerular filtration, and (b) increase in the tubular reabsorption of uric acid from the glomerular filtrate. But the uric acid clearance is often decreased while the filtration rate is normal. Therefore, the general factor in the reduction of the uric acid clearance in pre-eclampsia and eclampsia appears to be augmented reabsorption of uric acid by the renal tubules. This factor of increased tubular activity is expressed in the lowered clearance ratio of uric acid/inulin. As Fig. 1 shows, this ratio is decreased in every pre-eclamptic and eclamptic patient. Also, in every case, the ratio rises post partum while in normal patients there is no consistent direction of change with delivery.

The data of Schaffer, Dill, and Cadden[4] include simultaneous antepartum clearances of inulin and uric acid in eight normal and seven pre-eclamptic pa-

tients. The clearance ratios calculated from their data are presented in Fig. 2. Their absolute values are not comparable to ours for the reason already mentioned (diodrast). However, it is clear that the clearance ratio is decreased in their pre-eclamptics where it averages 0.23; a reduction of 24 per cent from the mean ratio in their normals which is 0.30.

Whether the decreased uric acid clearance in toxemia represents renal "impairment" is a dialectic question. All evidence indicates that the reabsorption of filtered uric acid, in the normal subject, is an active tubular process rather than mere passive back-diffusion, as in the case of urea. In toxemia, this reabsorption is augmented. Since the clearance ratio of urea/inulin is normal, increased back-diffusion through damaged tubules probably is not operative. The kidney would, then, seem to be overactive in the reabsorption of uric acid, rather than underactive.

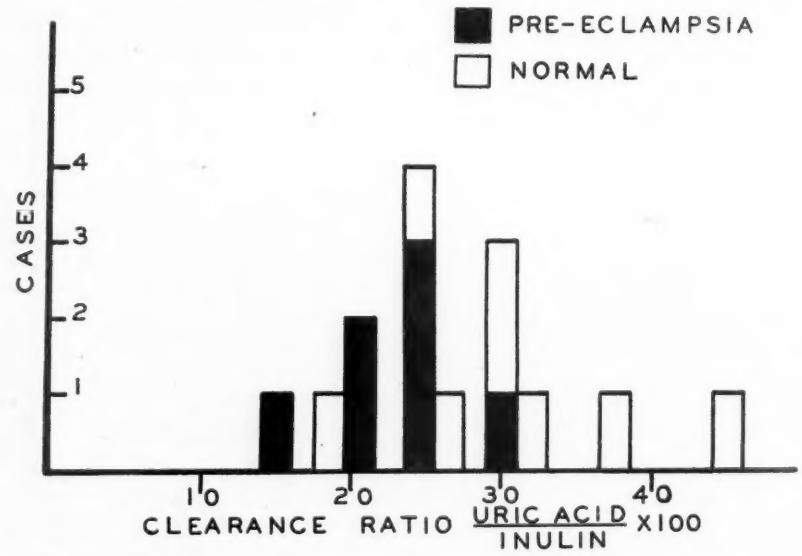

Fig. 2.—The $\frac{\text{uric acid}}{\text{inulin}}$ clearance ratios calculated from the data of Schaffer, Dill, and Cadden.[4] The average ratio for the normal patients is 0.30, and for the pre-eclamptics is 0.23.

The effect of pre-eclampsia upon the uric acid clearance may be more marked than is apparent from the percentage depression in the clearance. Brøchner-Mortensen[19] has shown that the uric acid clearance increases when the plasma level of uric acid is raised. Perhaps the spontaneous hyperuricemia of these toxemic patients also increases the clearances, and thus masks the true extent of the effect of the toxemia upon the renal tubule.

Our finding of a 25 per cent reduction in the urea clearance in pre-eclampsia is in accord with what other investigators have reported. At first sight it might seem to be in disagreement with an earlier paper by one of us,[22] which has been criticized by Herrin[23] for reporting normal urea clearances in pre-eclampsia. In that paper, however, it is stated: "In all groups, the higher or highest clearance of several shown by a patient was taken as that individual's functional level if certain conditions were fulfilled." We do agree with the majority that many pre-eclamptics will show somewhat decreased urea clearances on single tests. Some will show persistently lowered clearances on repeated tests, but others will vary well up into the normal range in at least one of a series of tests.

Summary and Conclusions

Simultaneous measurements were made ante partum of the serum clearances of inulin, urea, and uric acid in ten normally pregnant patients near term, and in ten patients with pre-eclampsia and eclampsia. In all but two of the normals, the tests were repeated post partum.

In pre-eclampsia and eclampsia, the uric acid clearance is reduced. In this series, the diminution averaged 50 per cent.

On the average, the reduction in uric acid clearance depends equally upon 2 factors, viz.: (1) a decrease in the rate of glomerular filtration, and (2) an increase in the tubular reabsorption of uric acid from the glomerular filtrate.

The increased tubular reabsorption of uric acid is the more general of the two factors.

Published data of other workers have been reinterpreted to support these conclusions.

The diminution in uric acid clearance appears adequate to explain the hyperuricemia of pre-eclampsia and eclampsia.

We wish to acknowledge our indebtedness to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters, who have permitted us to use their private patients, and who have read the typescript. The urea clearances and Duboscq colorimetry were done by Doris Furze and Eleanor Brudnicki.

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VAGINAL HYSTERECTOMY IN THE MANAGEMENT OF DESCENSUS UTERI*

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IN THE management of descensus of the uterus, today, two procedures are employed almost to the entire exclusion of all others. One of these is vaginal hysterectomy together with the use of the cardinal ligaments, the pubocervical fascia, the uterosacral ligaments, and the upper portions of the broad ligaments for the construction of a supporting structure which will uphold the vaginal vault and the bladder. The other is the Manchester operation, or one of its modifications. The latter, as it is usually done, employs the bases of the broad ligaments and the pubocervical fascia as the means of support, the cervix being nearly always shortened by amputation. Advancement of the bladder is an essential part of this operation. The intelligent treatment of uterine descensus requires a clear conception of the mechanics of uterine support and of the anatomy of the structures by which this is accomplished. The use of the round ligaments to hold up the stump of the uterus after subtotal hysterectomy long since demonstrated its ineffectiveness and the attachment of the cervical stump or the fundus of the uterus to the anterior abdominal wall has been an unsatisfactory procedure. To deal efficiently with descensus of the uterus, and the sometimes marked outlet relaxation which accompanies it, requires a greater operative skill and a better knowledge of pelvic anatomy than do many of the operations carried out abdominally.

In either method of operation, the restoration of support depends upon the use of these structures. Failure to use them, or failure to employ them properly, causes the operation to be a failure.

We have treated the greater part of our cases of descensus by vaginal hysterectomy. A smaller number have been dealt with by the employment of bladder advancement, anterior colpoplasty, and transplantation of the bases of the broad ligaments. To this has been added a perineal plastic operation varying in degree according to whether we were dealing with a simple rectocele or an enterocele.

In a little more than 600 vaginal hysterectomies we find that the operation was done for descensus of greater or less degree in 160 cases. All cases have been excluded in which the cervix did not come easily to the introitus with slight traction. These we refer to as descensus of the first degree. There were 36 of these. Those in which the cervix emerged from the introitus for a distance of not more than 2 inches were termed second-degree descensus. Of these there were 65. Those in which the uterus came out further, including those in which the entire length of the uterus came out, are termed third degree. This group numbered 59. In many of the cases of more extensive descensus an unhealthy cervix was found with decubitus, endocervicitis, and eversion. Occasionally small fibroids were present.

So far as technique is concerned, there were two groups of cases. In those in which the uterus was entirely out, or at least a large part of its bulk escaped from the vagina, we have used the method which is often spoken of as the Mayo operation and which has been well

*Presented before a meeting of the Chicago Gynecological Society, Oct. 20, 1944.

described by Ward. The operation as first described has been somewhat modified by Ward. In addition to the method as described by him we have found the use of the pubocervical fascia, dissected free in the early part of the operation and brought together over the united broad ligaments, to be a valuable part of the procedure and one which materially adds to support. An inverted T-shaped incision is made on the anterior wall extending nearly to the urethra.

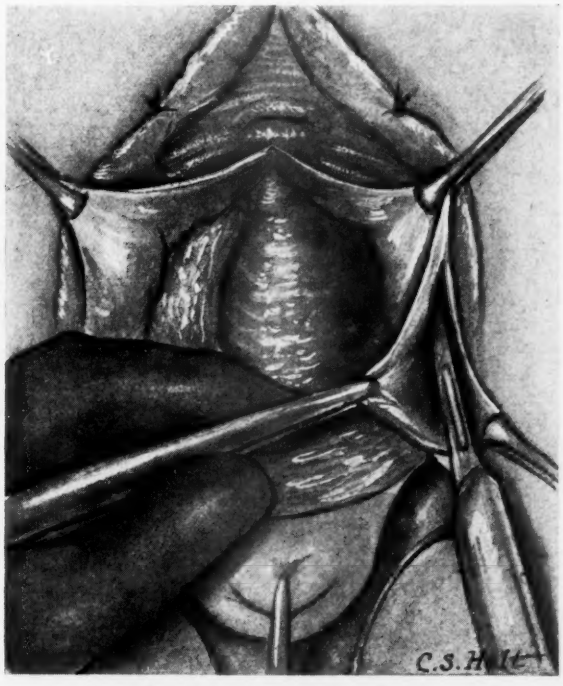

Fig. 1.—Dissection of the fascia of the anterior wall. Dissection complete on left.

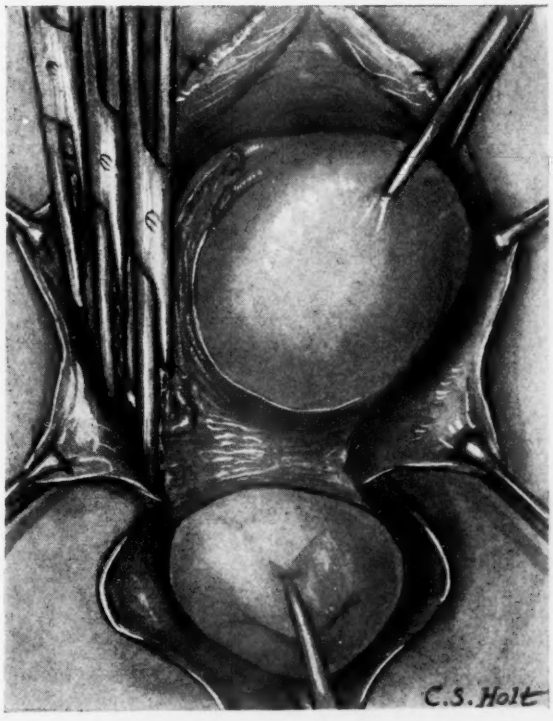

Fig. 2.—Broad ligament caught with three clamps and divided. Uterine artery visible.

Flaps are freed on each side and the fascial layer is carefully dissected free. This fascial flap is important and it should be gotten out as nearly intact as possible. We have tried both scissors and the knife for this step and believe the knife to be the better. The anterior peritoneal fold is then opened. The incision is extended around behind the cervix and the posterior peritoneal pouch is opened. The uterosacral ligaments are caught with short

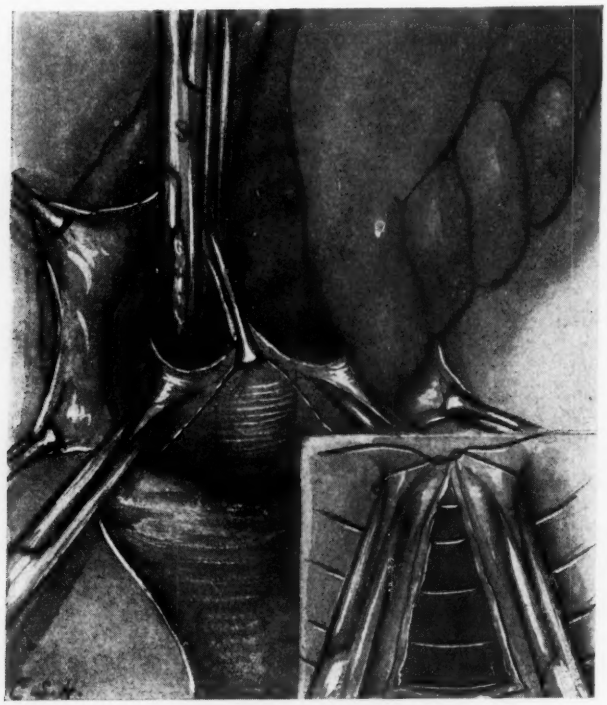

Fig. 3.—Clamps on uterosacral ligaments. Excision of redundant part of cul-de-sac. Closure of posterior hernia (inset).

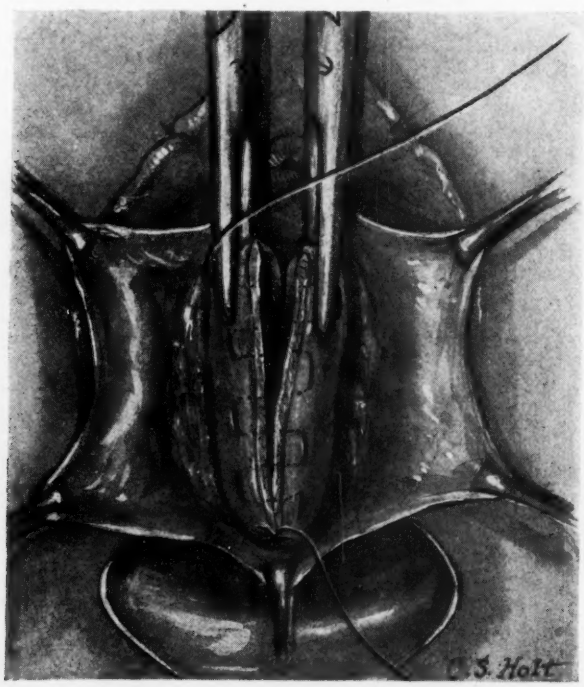

Fig. 4.—Broad ligaments are united from below upward. Clamps removed as suture progresses.

straight clamps and divided. The uterus is then turned out anteriorly and the broad ligaments caught in three clamps on either side. The uterus is then removed. The next step is to approximate the uterosacral ligaments. In patients in whom there is a marked enterocele it adds much to the efficiency of the operation to resect a portion of the uterosacral pouch, much as one might remove a part of the sac in a hernia. This step in the procedure was originally suggested by Ward. An efficient closure of the posterior part of the weakened uterine supports is a very important part of the operation. We have found that here is a frequent place for failure to manifest itself. Whether a part of the pouch is removed or not,

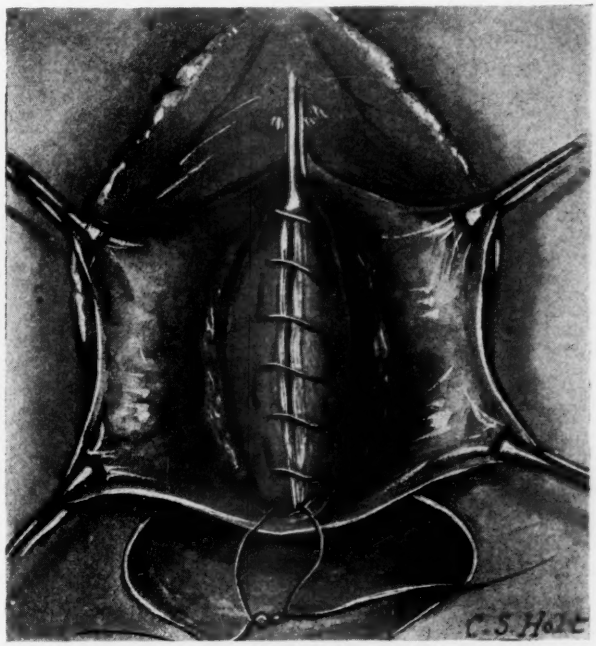

Fig. 5.—Suture returns re-enforcing closure.

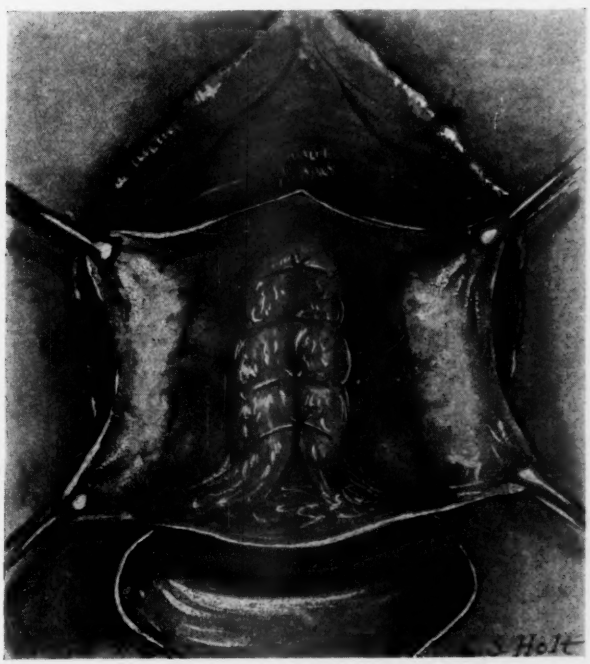

Fig. 6.—Fascial structure united by fine catgut sutures.

the uterosacrals are united with three, or perhaps four, transverse sutures. This closes the posterior part of the weakened area. The broad ligaments are then closed by means of a running mattress suture passed back of the clamps which are removed in succession from below upward as the suture proceeds. This suture is locked at the top and then, in the form of a running suture, is brought back to the point from which it started. This adds to the safety of hemostasis and brings the peritoneal surfaces into better apposition. The anterior edge of the sutured ligaments is then fastened below the rami of the pubes and as close to them as possible by means of a stitch on either side. This is to close the anterior gap and to prevent the bladder from escaping over the forward edge of the broad ligaments. If a gap remains between the uterosacrals and the hammock of broad ligaments, this is closed by suture. A firm floor has then been formed upon which the bladder may rest. Over this is sutured the pubocervical fascia, and, finally, the mucosa is closed after removing the excess portion. The pubocervical fascia and the mucosa are best closed with fine, No. 0 chromic gut used singly. This is fully strong enough and leaves less material to be absorbed. A perineal repair is done, the degree of which depends upon the degree of relaxation. The cure of enterocele depends upon the closure of the uterosacrals rather than upon the perineal plastic. It is essential to be able to distinguish between enterocele and rectocele. We have seen a number of patients in whose cases failure to make this distinction, which has led to an attempt to provide relief by the use of a perineal repair, has resulted in failure.

A variant of this procedure is utilized when the uterus does not come down far enough to be brought entirely out of the vagina. In these cases it does not come far enough out to render the use of the running mattress suture easy. Under these conditions the broad ligaments are caught in clamps, usually three on each side, ligated and divided. The uterus is brought out anteriorly or posteriorly as may seem easier. The ligated ligaments are then united in the median line and the pubocervical fascia is then brought together over them. The closure of the uterosacral ligaments is carried out just as has been described. This last method is well illustrated in the last edition of the textbook of Curtis.

Our experience has led us to emphasize a few points in operative technique. The closure of the posterior hernia which comes down through the interval between the uterosacral ligaments is extremely important. In our earlier cases, before we came to appreciate the necessity of this, we had some recurrences of the enterocele. If the uterosacral pouch of peritoneum is lengthened notably, it should be resected as one would do with a hernial sac. It is essential to close the anterior portion of the weakened area. Thus is accomplished by attaching the sutured broad ligaments, as has been noted above, as high as possible under the rami of the pubes. A careful perineal repair is essential. It is unnecessary, particularly in fascial approximation and in the closure of the mucosa, to use heavy catgut. We find that No. 0 chromic gut is fully heavy enough and believe that it has an advantage in that it leaves less to absorb. For all other work No. 1 gut, used singly, is amply strong. It is illogical to employ gut which has a tensile strength many times that of the tissue in which it is placed. Unnecessarily heavy gut places an unduly heavy burden upon the surrounding tissues as it requires them to dispose of a far larger bulk of material than is needed. The argument that heavy and long-lived gut is needed for hemostasis is erroneous. Thrombosis, upon which permanent hemostasis depends, is complete long before the end of the time needed for the absorption of the gut.

The removal of the uterus is particularly useful in patients in whom the descensus is marked. In our hands, operations of the Manchester type are used as a rule in cases in which the descensus is not too marked and in patients, of whom we have seen a goodly number, who have undergone subtotal hysterectomy elsewhere and in whom the cervix has subsequently come down. It may also be used in cases in which a previous laparotomy renders hysterectomy difficult. Often an incidental condition has been cared for while the existing descensus had been ignored or treated by some inadequate method intra-abdominally. We have also seen a number of patients who had had an attachment of the fundus to the abdominal wall with a sbsequent and sometimes very marked descensus.

In many women with marked descensus the uterus is an unhealthy organ. Endocervitis is common, and, if a procedure of the Manchester type is done, after amputating a sufficient length of the cervix, little is left of the uterus. Myomas are often present and, in our laboratory, adenomyosis is sometimes found. The excision of the uterus permits of a more efficient use of the broad ligaments which may be interposed under the bladder, and which, when reinforced by the pubocervical fascia, form an efficient support. In these cases there is always a herniation of the posterior part of the upper pelvic floor. This can be much better dealt with after the uterus is out than when it is not removed. The Manchester operation does not include suture of the uterosacral ligaments. This posterior

repair is one of the most important parts of the operation, and, if not well done, will result in a recurrence in the form of a posterior herniation.

In the fetus the rectouterine pouch extends to the level of the levator ani. This depth decreases with age until the lowest point of the cul-de-sac is at the level of the second or third sacral vertebra. A persistent pouch of the fetal type may predispose to descensus. Descensus which occurs in nonparous women probably is due, at least in many cases, to this congenital condition. It has not been possible to obtain follow-up data concerning all of the patients upon whom this operation was done. Some of them were patients in the ward service and not all of them were altogether cooperative. There were a number whose homes were outside of Chicago, sometimes at a considerable distance, and these could not be accurately followed up. We have felt that letters addressed to patients are not wholly to be relied upon and replies may indicate a result either better or worse than would be revealed by actual examination. Most of them, however, were seen by the member of the staff who carried out the operation. One statement must be made in considering the end result. The type of vaginal hysterectomy done for conditions other than marked decsensus need not shorten the vagina. In a large series of these we have found it quite possible to maintain a normal depth. In those done for descensus, especially those in which the uterus has emerged partially or wholly from the introitus, the vagina is already shortened. The descending uterus brings with it the anterior and posterior walls. Shortening has already taken place. In some of these patients there is some shortening after operation. In most of them it is not extensive enough to cause any complaint and many of the patients are elderly women. In many of them shortening is not noticeable. In estimating the value of the end result we have been concerned as to whether the vaginal vault is well supported, the anterior vaginal wall held firmly up, with relief of incontinence if it was present before the operation, and particularly whether the posterior portion of the vault semed firmly held. Our poor results have ranged from a complete eversion of the vagina, of which there has been but one, to slight relaxations of the anterior wall, causing more or less cystocele or urethrocele.

In the less advanced cases of descensus, those of Group 1, we were able to follow 26 accurately. Success was attained in all but one. In this group of cases the problem is less difficult than in those on which the uterus protrudes and the supporting structures are greatly thinned. The material with which to work is of better quality and a firm support is more easily constructed.

Of the patients making up Group 2, 32 reports were obtained as to the end result. Of these 28 were satisfactory and 4 were not. In one of these the end defect was a urethrocele which the examiner described as small. It could not be called an ideal result inasmuch as some of the anterior repair had not held, yet the patient was quite comfortable.

In cases in which incontinence was a symptom, an attempt to correct this was made, usually by the use of the Kelly procedure. This is easily combined with the anterior colpoplasty.

In Group 3, those in whom the uterus came out more than 3 inches, there were 53 cases in which adequate reports could be had. Of these 38 were satisfactory. As these patients have been more inconvenienced by the descensus than those in which it was of a less advanced type, it is especially desirable to give them relief. In 15 cases failure of greater or less degree occurred, one being a total eversion. This patient was a woman well on in years. The problem was ultimately solved by a colpectomy. We have had no experience with the attachment of the vaginal vault to the anterior abdominal wall as advocated by Brady.

In estimating unsatisfactory results we have included all cases in which any degree of cystocele persisted or in which any degree of enterocele was apparent. Most of them were quite comfortable.

The operation has the great advantage of being quite safe. One death occurred in this series, giving a mortality rate of 0.6 per cent. This is the only death in a series of over six hundred vaginal hysterectomies done for all causes. The mortality in the entire number of vaginal hysterectomies is 0.16 per cent. The operation in the more advanced cases of descensus is almost extraperitoneal. It may be done by an experienced operator in less than an hour and is withstood very well indeed even by women of advanced years. It shares this factor of safety with the Manchester operation but has, I believe, the advantage of giving a more complete support inasmuch as the posterior portion of the upper pelvic floor may be dealt with. The competition between the two procedures should be limited, it seems to me, to cases in which the descensus is not extreme, better when the cervix has not passed the introitus. In 12.5 per cent of our cases, or 20 in number, the result was not altogether satisfactory. In 87.5 per cent the result was satisfactory. By this we mean that a good anatomic result was

attained, that is, a flat and well-supported anterior wall, a complete cure of enterocele, and a well-healed perineum. Many women whose operations might permit criticism concerning the anatomic result were quite happy, satisfied, and relieved of symptoms.

Aftercare is quite simple. A vaginal pack is put in for twenty-four hours. This is used less for hemostasis than for support. The abdominal binder after a laparotomy supports the abdominal wall when the patient vomits or strains in any way. The vaginal pack serves a similar purpose. The bladder is emptied by catheter before the patient is removed from the table. Catheterization is done after twelve hours unless the patient complains of discomfort sooner. Thereafter the bladder is emptied every eight hours until she voids spontaneously. When the bladder empties itself, a test catheterization is done to ascertain whether it empties itself completely. If less than 30 c.c. is obtained, the use of the catheter is discontinued. If the amount is greater than this, the eight-hour schedule is maintained until the amount after catheterization is less than 30 c.c.

The convalescence in the majority of these cases is uneventful. Distention is, as a rule, minimal, and in many cases bladder function returns soon after operation. Some bladder irritability may persist for a time after operation, which is due to the dissection of the bladder base from the anterior surface of the uterus. The greatest single discomfort which these patients seem to have is caused by the stitches in the perineum which close only the skin. Morbidity, as reckoned by the standard of the American College of Surgeons, is high. In the entire series we found that 53.3 per cent had fever on two or more days, excluding the first, the temperature rising to 100.4° F. or more. The extensive dissection which is needed, opening up considerable areas, can scarcely avoid giving rise to some absorption. Recovery, in most cases, gave very little trouble.

In one case death occurred. This patient was a woman in whom the protrusion was about 5 or 6 cm. She went through the operation well but got out of bed the first night and was controlled with some difficulty. She developed a pelvic inflammation and shortly thereafter a pneumonia. The latter was the determining cause of death.

Summary

Vaginal surgery requires a definite knowledge of the anatomy of the region in which the procedure is carried out. It also demands a familiarity with the technique of the operations which are done in this field. The specialist in pelvic surgery should be familiar with both the anatomy and technique, for the results of operations for descensus done from below are so much better than those following abdominal procedures that the latter should give way entirely. The safety of the operation done from below is greater and this fact should weigh heavily in the choice of procedure. It is our opinion that vaginal hysterectomy, rather than the procedures of the Manchester type, particularly in cases of extreme descensus, is the operation of choice. In cases in which the descensus is of moderate degree, either will serve. As in many patients the uterus has passed its usefulness, and especially inasmuch as the cervix is often unhealthy, we believe that removal of the uterus has a much larger field of usefulness than the alternate procedure.

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Discussion

DR. N. S. HEANEY.—When I was asked to discuss this paper the title was given to me as "Vaginal Hysterectomy and Prolapse of the Uterus," and I prepared a discussion along these lines. When I came to the meeting I found that the paper was on "descensus." We do not use the term descensus. The patient has a prolapse when the cervix comes out of the vagina, up to complete eversion of the vagina or procidentia.

In my mind there is no place for the Manchester operation in the treatment of prolapse of the uterus unless it be combined with bladder advancement which is not a part of the Manchester operation. Anybody who adds bladder advancement to the Manchester operation does something that is useful because that is the particular part of the operation that is efficient.

Dr. Danforth has now had one death in something over 600 cases. I have done vaginal hysterectomy ever since I first started to practice and I have taken statistics only during

less than half of my experience. During this week we completed 1,237 vaginal hysterectomies with some three deaths. Had I started when Dr. Danforth did I would have 675 without a death, because we have done 675 since the last death.

Dr. Danforth uses the technique of the Mayo operation. The Mayo operation was described some twenty-five or more years ago and there should have been some improvement found in this length of time.

Dr. Heaney then quoted extensively from a previously published paper ("Vaginal Hysterectomy in Cure of Prolapsus Uteri") in which his method was described.

DR. JOSEPH L. BAER.—We published an article in 1928, the opening paragraph of which was as follows:

"The choice of operation is influenced first by limitations of conditions in the individual patient; second, by the operator's familiarity and perhaps success with particular types of operation; and third, his desire to improve results through the utilization of other methods."

The publication of 1928 showed 11 types of procedure for the cure of prolapse among 220 operations. The interposition operation was employed 91 times, suspension and vaginal reconstruction in fertile women was employed 14 times, the Le Fort operation 14 times, extravaginal reposition 13 times, vaginal hysterectomy 7 times. In 1937, 221 operations were reviewed, which showed the shifting trend of our clinic group at Michael Reese Hospital. One hundred sixteen patients were treated by vaginal hysterectomy and only 30 by the interposition operation; 29 by the Le Fort operation, 13 by the Gilliam suspension and parametrial fixation; there were 9 instances with us of the Manchester operation. In 1939, Dr. M. L. Leventhal reported on 51 Manchester operations. We had a veritable rush of Manchester operations because we were all enthusiastic about them. Examining the data for 1944 from January 1 to October 14, we found that vaginal hysterectomy was performed 127 times, the Manchester or parametrial fixation 8 times, the Neugebauer-Le Fort, 5 times, and not a single Gilliam or Kocher extraperitoneal fixation. So we have come to vaginal hysterectomy as the outstanding cure for prolapse.

The essayist has further confused the classification of prolapse. The essayist would have the first degree as that stage in which the cervix can easily be brought by traction to the introitus; the second degree, the condition in which the cervix emerges not over 2 inches; the third degree, with the cervix completely down. In the body of the paper, however, he speaks of Group 3 as those cases in which the uterus is out more than 3 inches.

The alleged purpose of a vaginal pack after operation, is support, and comparison is made to an abdominal binder which supports the recently opened abdominal wall in laparotomy. Of course we know that in spite of an abdominal binder or corset or any other abdominal device, if the patient is going to have an evisceration neither corset nor binder is going to prevent it. By the same token a pack left in the vagina for twenty-four hours, to my way of thinking, is merely a foreign body which serves no useful purpose and interferes with proper drainage of the serum discharge or such bloody discharge as might otherwise escape and not become infected.

The essayist uses eight-hour catheterization technique for the bladder after the first period of twelve hours postoperative. My present leaning is toward a permanent catheter, provided it be a small type which stays in situ without having to be repeatedly reinserted. A catheterization twelve hours after operation is not too long an interval unless the patient is receiving an abundance of parenteral fluids, in which case the bladder is going to be more than full and should be emptied as required.

The essayist's technique is precise, sound, and excellent except for the use of a continuous mattress suture for the control of the uterine artery, which I do not like. I am sure Dr. Danforth is continuing it because so far he has had no disaster, but I submit that disaster will come.

Dr. Danforth mentions 15 failures in a total of 53 cases, a percentage of 28. That is a high percentage of failures to register in a group of women without any subjective symptoms. I am not willing to accept that high percentage of failure as an acknowledgment of failure of his work. In our original report on the interposition operation, we had 12.5 per cent failures, on the basis of which we have practically discontinued the interposition operation.

Dr. Heaney states there is no place for the Manchester operation in prolapse unless bladder advancement be carried out. If he chooses to limit the word prolapse to those instances in which the entire uterus is out, which, of course, is not the connotation of the word prolapse, then I shall not quibble with him. But certainly there is a place for parametrial

fixation in lesser degrees of prolapse and it does not require advancement of the bladder. The Manchester operation is calculated to achieve its result by anchoring the cervix. Irrespective of what one does with the bladder, there is still a place for the Manchester operation. I caution Dr. Heaney against further use of pituitary preparations for the control of bleeding. We have discontinued their use entirely. We have had disturbing conditions on the operating table following the use of pitressin or its modifications.

Finally, Dr. Heaney stressed the importance of bringing the round ligaments down and approximating them in the midline at the maximum tension that can be put on them without avulsing them. Unfortunately those women have a very uncomfortable postoperative course. The traction on the round ligaments is a source of bilateral pain in the groins which persists until the fixation lets go.

DR. ROBERT M. GRIER.—When I first started with Dr. Danforth in 1924 practically all of his hysterectomies were subtotal. The argument for this was that the postoperative mortality was too high in the total operation, due to infection. We used to have a great many women with cystocele, rectocele, and descensus, and for these we usually did a two-stage operation, repairing the cystocele and rectocele with a Sturmdorff operation on the cervix, and then through a laparotomy incision the uterus was removed.

In 1927 Dr. Danforth became quite concerned because of some failures. He tried the interposition operation on patients with severe cystocele, but this was given up. Then, I believe due to the influence of Dr. Heaney, he did more and more vaginal hysterectomies. The question became, how large should the uterus be before the vaginal operation was inadvisable? Now we avoid its use when the uterus is as large as a four months' pregnancy or even less. We do vaginal hysterectomies for those cases where there is a pronounced cystocele nad rectocele and the uterus is not too large. The Ward technique came into use and we began to unite the round ligaments under the pubic arch for severe cystocele after doing a vaginal hysterectomy.

Then, I think due to the Mayo Clinic influence, we found we could do total abdominal hysterectomies without as high a mortality as was thought. We now do more of them and reserve vaginal hysterectomies for marked prolapses. At Evanston Hospital we do more total abdominal hysterectomies than any other type but we still do vaginal hysterectomies for procidentia and outlet relaxation. We thus do fewer subtotal operations but a good share of vaginal hysterectomies.

DR. DANFORTH (Closing).—These 600 vaginal hysterectomies cover a period of about ten years. I think that what we term the Mayo operation probably was first done by Riddle Goff but he did not publicize it adequately. Dr. Charles Mayo was the one who made public the worth of the operation and that is why it has his name.

It is interesting to hear Dr. Baer state that in this year's work at Michael Reese Hospital they have come back to vaginal hysterectomy after having given it up for a very considerable time in favor of the Manchester operation.

As to the criticism of the running mattress suture I can only say that we have used it in a large number of cases and have had no bleeding. The only bleeding we have had after total abdominal or vaginal hysterectomy has been bleeding from the vaginal vault.

BILATERAL POLYCYSTIC OVARIES*

Significance in Sterility

IRVING F. STEIN, M.D., F.A.C.S., CHICAGO, ILL.
(From the Michael Reese Hospital)

BILATERAL polycystic ovaries are associated with a definite clinical syndrome, the significance of which is not generally acknowledged by gynecologists. The characteristics of this syndrome are menstrual irregularity featuring amenorrhea, a history of sterility, masculine type of hirsutism, and, less consistently, retarded breast development and obesity. Extreme masculinization is sometimes noted in addition to hirsutism and there may be facial acne. Pelvic pain is not a consistent symptom, but is one which occasionally causes the patient to present herself for examination. The ovaries are similarly and simultaneously enlarged but are difficult to palpate; therefore pneumoroentgenography is of great value in establishing or corroborating the diagnosis. The cure of bilateral polycystic ovaries requires surgical treatment.

It is fifteen years since we first performed wedge resection of bilateral polycystic ovaries for the relief of prolonged amenorrhea and/or sterility. Two previous publications[1, 2] have been presented. This communication represents the third five-year report on this subject. When we made our first contribution on this subject in 1935, the syndrome associated with bilateral polycystic ovaries was a new concept in gynecology. Since then, we have emphasized its importance in the study of sterility. We stated then, and are still convinced, that the development of this condition is not congenital; neither is it inflammatory nor degenerative. It is the result of a definite endocrine disturbance.

Amenorrhea is a conspicuous feature of the clinical course in these patients. One group never menstruated. Another showed mere staining or a very scanty flow which continued throughout adolescence and which developed into complete amenorrhea. These patients never really menstruated in the physiologic sense but had scant and probably anovulatory bleedings. No true menstrual cycle was ever established in this group. The largest group of patients had secondary amenorrhea and irregular periods.

The amenorrhea is often preceded by a history of normal menstrual cycles which may extend through adolescence and even into early maturity when irregularity and missed periods usually occur. The irregularity may at first be noted as a hypermenorrhea to be followed after variable lengths of time by increasingly longer periods of amenorrhea. These periods may at first consist of lengthening intervals interrupted by scanty uterine flow. Then the interval may be for two, three, or six months, interspersed with an occasional apparently normal menstrual period. Ovulation may occur once or twice a year followed by a normal period. In other cases, as we have previously reported, periods of amenorrhea had been absolute from two to eight years, continuing until surgical correction of the ovarian pathology was accomplished. In rare instances normal sex cycles were initiated at puberty and continued for some years, and even a pregnancy occurred before there was evidence of cyclic disturbances, such as amenorrhea and secondary sterility. In all of the instances described above, the functional disturbances of the reproductive tract were in association with

*Presented before a meeting of the Chicago Gynecological Society, Oct. 20, 1944.

the development of bilateral polycystic ovaries. Where these ovarian changes occurred early in the reproductive life of the individual, uterine hypoplasia was usually found. In the cases of secondary amenorrhea, however, the uterus was normal in size unless the amenorrhea had persisted for long periods (two to eight years) when a definite diminution in uterine size, or even atrophy, occurred. In regard to the secondary sex characteristics, they are of two types: the true feminine, and those which are characterized by masculinizing effects.

Hirsutism occurred in fully 50 per cent of our patients, but it varied a great deal in distribution and extent. In some of the adolescent patients the beard was so heavy that it required frequent shaving and the arms and legs were also markedly hairy. In many cases there was a sternal hairy growth with rings of coarse hair about the areolae of the breasts and a masculine type escutcheon. The vulvar hair was coarse in texture and was thick. Voice changes have not been conspicuous but there were two adolescent patients with marked hirsutism and virilism whose voices were noticeably deep. The feminine type exhibited no abnormal hair distribution.

Breast development varied considerably, from the fully developed feminine type to marked hypoplasia, and there was no definite relationship between breast development and hirsutism. In one case of primary amenorrhea there was practically *no visible breast development:* a mere papulelike elevation represented the nipple. A most remarkable and rapid development occurred in this patient after surgical treatment of the ovaries. The breasts enlarged and the nipples and areolae developed noticeably in a few months. After marriage and the birth of a child, lactation occurred and the patient was able to nurse her child successfully.

Obesity was present in approximately 10 per cent of our patients in this series. At first we had considered this as characteristic of the syndrome, and so stated in our original report. The basal metabolic rate in these patients was always within the normal range, however, and it is likely that obesity is no more common in this than in other gynecologic conditions.

Diagnosis

Bilateral polycystic ovaries are frequently unrecognized on routine pelvic examination as they are difficult to palpate. This may be true because more than one-third of our patients were single girls in whom a digital examination was limited to rectoabdominal palpation, which as a rule is not conclusive. In obese women, and in those who were rigid and tense, or in patients in whom the ovaries were of the "oyster type," palpation proved to be unsatisfactory and a presumptive diagnosis was made until more accurate and reliable methods could be employed. Because of the difficulty encountered in regularly palpating the ovaries in this group of women, gynecography was utilized for diagnosis.

There are very definite clinical indications which lead to the *presumptive diagnosis* of bilateral polycystic ovaries, such as the history of amenorrhea and/or sterility, and the discovery upon general physical examination of a masculine type of hirsutism, and in many instances, hypoplasia of the breasts. Pelvic examination will often reveal the presence of a small uterus. While in some women we can palpate definitely enlarged and globular ovaries, in the great majority we fail to find any abnormality and rely upon pneumoroentgenography. Here in gynecography we have a simple and positive method of diagnosis, so conclusive in its information as to be the deciding factor before laparotomy is performed. It is noteworthy that in every instance where this

diagnostic method was employed and bilateral polycystic ovaries found on the films, corroboration was obtained at the time of surgery.

Gynecography has proved to be the mainstay in diagnosis, not alone for recognition of ovarian enlargements which escape palpation, but also for a true evaluation of the pelvic status. Uterine hypoplasia is often present and is readily recognized by this means. Normally, the uterine shadow upon pneumoroentgenography is about four times the size of the ovarian shadow. In the condition under discussion, however, the ovaries may appear half as large or even the same size as that of the uterus. The ovaries may appear to be round, oval, elongated, or angular on the film, depending upon the position of the gonads in the pelvis at the time of x-ray. It should be noted that the prone, modified knee-chest posture is assumed for the x-ray and the film records a projected shadow from one aspect only (Fig. 1); the ovary may be suspended so that it presents its broad or narrow diameter for projection on the film. Hence, one ovary may appear round and the other oval, and one may appear much larger than the other, even though they are approximately the same size. The bilateral and symmetrical involvement of the ovaries is in itself a valuable diagnostic sign. Interpretation of the film requires experience (Figs. 2 to 7).

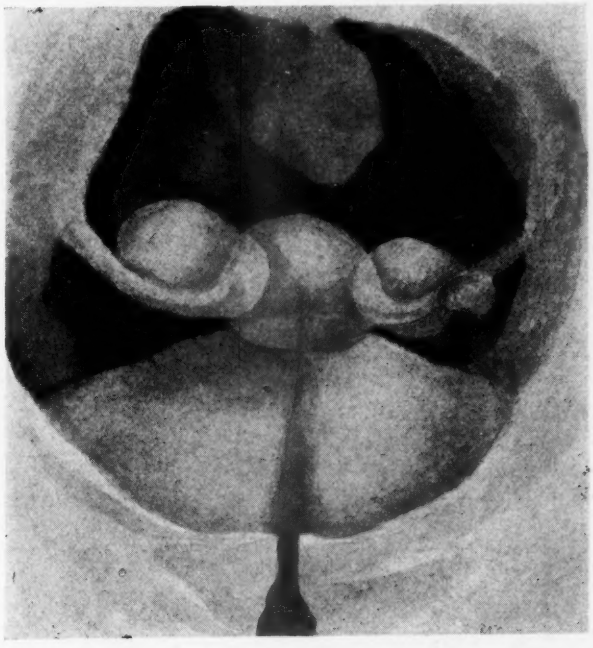

Fig. 1.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries. Difference in shape and size on film due to lateral and end views. Diagnosis: Bilateral polycystic ovaries.

For purposes of establishing tubal patency or obstruction, and for abnormalities of the uterine cavity, hysterosalpingography (utilizing opaque media) is valuable, but pneumoroentgenography is superior for recognition of ovarian and uterine enlargements. The two methods just referred to comprise gynecography.[3]

Earlier in our study, the basal metabolic rate was frequently estimated, especially in those cases where obesity was present, but as it was found to be within normal range in all of these patients, it was no longer considered of diagnostic value. In a considerable group of our patients, routine vaginal

smears and endometrial biopsies were taken. In cases of prolonged amenorrhea, the vaginal spreads showed a typical menopausal pattern for the most part. The biopsies as a rule revealed no significant data. It was difficult to determine when the biopsy should be obtained, inasmuch as the cycles were irregular and in some cases absent. If the biopsy were taken at the beginning of what proved to be a normal period, it would reveal a secretory phase, inasmuch as occasionally, perhaps once or twice a year, ovulatory cycles did occur. We are

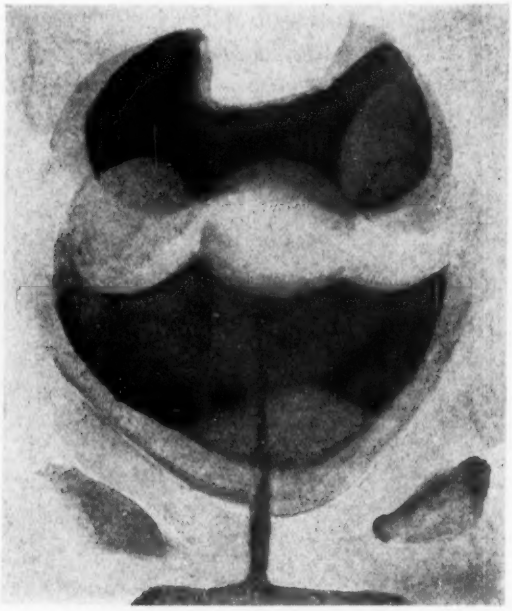

Fig. 2.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries, equal size and shape. Diagnosis: Bilateral polycystic ovaries.

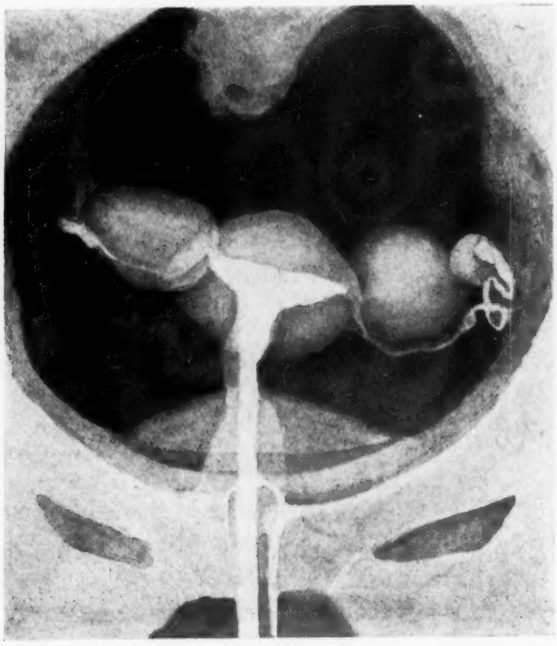

Fig. 3.—Combined gynecography. Bilateral symmetrical involvement of ovaries (each about 2/3 size of uterus). Diagnosis: Bilateral polycystic ovaries.

convinced, however, that most cycles in patients with bilateral polycystic ovaries are of the anovulatory type, as evidenced by the histories of menstrual irregularity and the long periods of sterility. Sugar tolerance tests and x-rays of the pituitary were done in a number of our earlier patients but no findings of significance were obtained.

Summarizing, the most significant data in establishing a diagnosis are: a history of primary or secondary amenorrhea; a history of sterility; a male

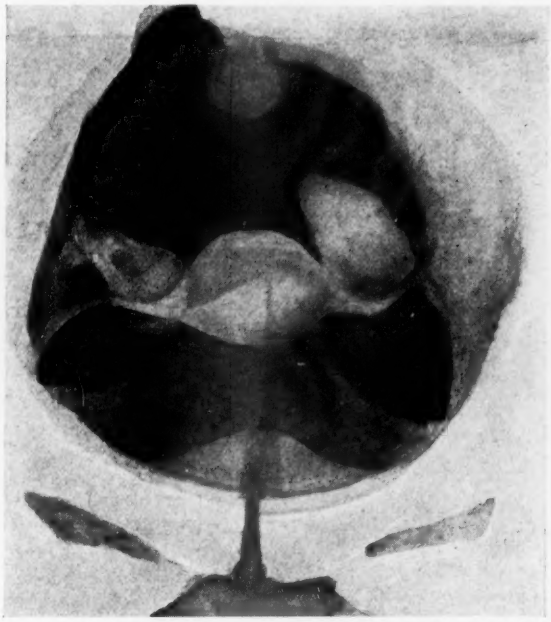

Fig. 4.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries. Diagnosis: Bilateral polycystic ovaries.

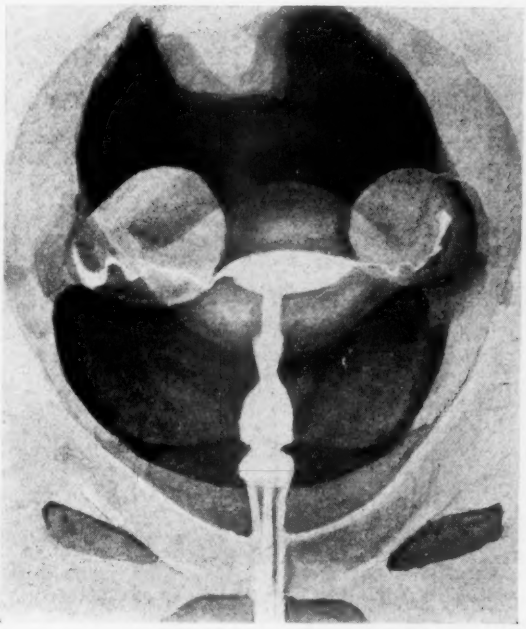

Fig. 5.—Combined gynecography. Bilateral involvement of ovaries. Right ovary larger. Uterus and tubes normal. Diagnosis: Bilateral polycystic ovaries.

Fig. 6.—Hypoplastic uterus. Bilateral ovarian involvement. Left ovary larger. Diagnosis: Bilateral polycystic ovaries.

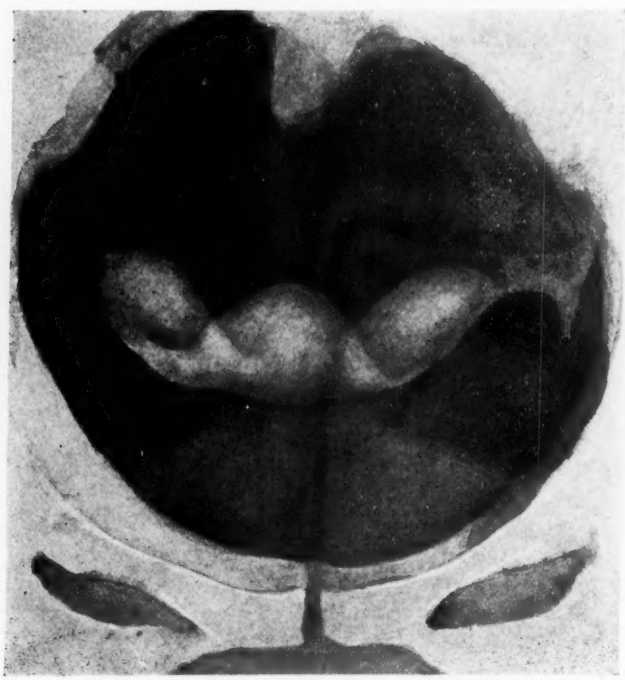

Fig. 7.—Hypoplastic uterus. Typical symmetrical ovarian enlargement. Diagnosis: Bilateral polycystic ovaries.

type of hirsutism; breast changes; and the finding of bilateral ovarian enlargements (corroborated by gynecography).

In the past fifteen years, we have studied 53 patients in whom the diagnosis of bilateral polycystic ovaries has been made, corroborated by gynecography and treated by bilateral ovarian wedge resection. These patients consisted of 23 single and 30 married women. Of the 23 single girls, amenorrhea occurred in 19, irregular bleeding in 3, hirsutism in 13. Four of them complained of pelvic pain. In only 2 was obesity present. In the married group, 24 of the 30 women complained of amenorrhea, 2 had irregular bleeding, *22 presented themselves because of sterility.* Hirsutism was found in 12, obesity in 4; only 8 in this group complained of pain (Table I).

TABLE I. ANALYSIS OF SYMPTOMS AND FINDINGS

NO.	STATUS	AMENORRHEA	BLEEDING	STERILITY	HIRSUTISM	PAIN	OBESITY	X-RAY GYNECOGRAPHY*	OPERATIVE FINDINGS
23	Single	19	3	0	13	4	2	22 B.P.O. 1 Myoma	23 B.P.O.†
30	Married	24	2	22	12	8	4	26 B.P.O. 4—No X-ray	30 B.P.O.† 1 Myoma 1 Granulosa

*Pneumoperitoneum.
†B.P.O. = Bilateral polycystic ovaries.

In analyzing our findings, of the 23 single girls gynecography was obtained in all but one case. Twenty-two showed bilateral polycystic ovaries, one in association with a small myoma (history of bleeding). One film was not diagnostic. Bilateral polycystic ovaries were found at operation in all of the 23 patients. Six had received hormone therapy previously without benefit. In all 23, menstrual cycles were established postoperatively. Usually a normal monthly rhythm occurred and the secondary sex characteristics were definitely influenced, favoring the feminine type. In some of the cases, however, the cycles in the first year following operation were irregular and sometimes prolonged. In three of the patients, inflammatory adhesions occurred with development of a cyst in one ovary. However, *the original condition of bilateral polycystic ovaries did not recur in any case.*

In the married group, 26 of the 30 diagnoses were verified by gynecography. At laparotomy, bilateral polycystic ovaries were found in all of the 30 women, one of whom had an associated myoma and one a granulosa-cell tumor. Ten women had previous hormone therapy with no improvement. After bilateral ovarian wedge resection, all of the 30 women had re-establishment of the menstrual cycle. There were no recurrences in this group (Table II).

TABLE II. ANALYSIS OF TREATMENT

NO.	STATUS	MEDICAL		SURGICAL	
		HORMONE	RESULTS	RESECTION	RESULTS*
23	Single	6	Negative	23	Positive
30	Married	10	Negative	30	Positive

*See Table III.

For ultimate evaluation of the surgical treatment of this condition, the restoration of the reproductive function, particularly in those patients who complained of sterility, is paramount. Of the patients who were single at the time of the ovarian wedge resection, three were subsequently married, all became pregnant, one of them giving birth to two children. Twenty-four of the married women had regularly recurring menstrual cycles, four were irregular, and in two

there was no follow-up. Among the 28 who were followed, 17 of the patients became pregnant. There were 31 women (28 from the married group and 3 from the single group who subsequently married) who were endeavoring to become pregnant. Twenty patients (64.5 per cent) became pregnant, resulting in 26 pregnancies and 28 babies; four were pregnant twice; one was pregnant three times; there were two sets of twins (Table III).

TABLE III. RESULT OF SURGICAL TREATMENT

NO.	STATUS	MENSES		NO. OF PATIENTS PREGNANT	TOTAL PREGNANCIES	RECURRENT CYST
		REGULAR	IRREGULAR			
23	Single	15	4	3‡	4	3*
			3†			
30	Married	24	4	17	22	0
			2†		2 sets of twins	
Total 53§		39	8	20	26 preg. 28 babies	3

*Inflammatory adhesions—cyst.
†No follow-up.
‡Subsequently married.
§60 (7 additional operations).

We repeat, for emphasis, that in no case was there a recurrence of bilateral polycystic ovaries. In 3 women in the single group, however, a unilateral cyst of inflammatory origin occurred, causing pain and menstrual disturbance.

Discussion

The normal sex cycle is dependent upon the harmonious interaction of the pituitary gland, the ovaries, and the other glands of internal secretion. Physiologically, ovulation occurs periodically and usually at a monthly rate, beginning at puberty and ending with the menopause. It is generally believed that ovulation occurs alternately when both ovaries are present, and if one ovary is removed, the monthly cyclic process continues in the remaining ovary. As there are probably two or three hundred thousand primordial follicles in the ovaries at birth and only one comes to maturity about the time of puberty and monthly thereafter, there is a sort of order or succession in which the follicle is sensitized and responds to anterior pituitary stimulation. When the endocrine function is disturbed and hypersecretion of the pituitary occurs, it is possible that a number of immature follicles may be simultaneously stimulated in both ovaries and that this process may result in an accumulation of multiple cystic follicles in the ovarian cortex. The prepubertal ovary appears somewhat similar but lacks the pathologic aspects of bilateral polycystic ovaries; in the group of young women who have never menstruated, there may be a continuation of the prepubertal state, i.e., amenorrhea and immature secondary sex development as a result of hyperpituitary effects upon the ovary. This eventually produces the typical pathologic effect in the ovaries. In women who apparently developed normally at puberty and during adolescence and in whom secondary amenorrhea occurred, the development of multiple follicle cysts in the cortex of both ovaries gradually transforms the ovaries into enlarged, smooth, and typically polycystic gonads. In both instances, normal function such as ovulation is suspended, or at best, occurs but rarely. Hence, amenorrhea and sterility usually obtain.

Both amenorrhea and uterine bleeding may, according to Zondek,[4] be due to hypersecretion of the anterior lobe of the pituitary gland wtih no correspondingly characteristic lesion of the ovaries. If this stimulation con-

tinues over a long period of time, eventually histological changes appear in the ovaries, characterized by multiple follicle cysts, a thickened capsule, and an increased fibrosis of the stroma of the ovaries. The cysts vary in size from a few millimeters to 1 centimeter in diameter, and may be lined by a single layer of granulosa cells, but the more advanced ones are lined only by theca cells. The cysts are usually limited to the cortex and, although almost always filled with an estrin-containing liquor, are usually functionless. There is probably no absorption of estrin from these cystic follicles which have become pathologic. If corpora lutea are found, they are few in number, as there are seldom normal Graafian follicles which come to full maturity. Therefore, the surface of the ovary, instead of being irregular with contracted corpora albicantia, is smooth, pearly gray in color, and contains small telangiectases.

In all women there are both estrogenic and androgenic effects from the ovary. Normally the estrogenic is sufficiently excessive to counterbalance any androgenic effect there may be. Hence the usual feminine secondary sex characteristics. When the estrogen-androgen balance is upset, there may be an inhibition of feminizing effects, and when the androgenic secretion is excessive, definite masculinizing effects result. This is evidenced by the masculine type of hirsutism and, in some cases, by virilism.

The fact that ovulation rarely if ever occurs in patients with well-developed bilateral polycystic ovaries may be explained by a mechanical theory. The enlarged and increased number of cysts crowding the ovarian cortex and covered by a thick ovarian tunica may, by pressure, prevent the primordial follicles in the stroma from maturing and secreting their hormones. If rupture of the Graafian follicles does occur, it may do so into an adjacent follicle rather than through the thickened capsule of the ovary. Furthermore, a fibrosis of the tunica and stroma compresses and obliterates the blood vessels which normally would carry the hormone secretions (Levine[8]).

After changes in the ovary have been established, hormone therapy is of no benefit. It is our belief that the good results in cases of amenorrhea, such as reported by Frank et al.,[5] Rubin,[6] Kaplan,[7] and others, have been obtained in patients in whom the ovarian changes had not yet reached the stage of cystosis. At least none of these authors has demonstrated, either by gynecography, surgery, or otherwise, that the patients whom they successfully treated with hormone or x-ray therapy had bilateral polycystic ovaries. We furthermore would like to emphasize that a differential diagnosis should be made utilizing gynecography, to exclude bilateral polycystic ovaries, before treatment for amenorrhea and/or sterility be administered medically (hormone, x-ray, vitamin therapy, etc.).

In our second publication,[2] we presented case abstracts and described in detail the pathology found in the ovary. Inasmuch as there is a great similarity in the additional cases which we are reporting at this time, we believe it unnecessary and of no increased value to the contribution to add these data. Therefore, we are summarizing the entire fifteen years' series which we have studied and followed.

We have shown in our previously reported 28 patients who were treated by bilateral wedge resection of the ovaries that physiologic function was restored by surgical means, as evidenced by the return of periodic menstruation and by a considerable number of pregnancies. We now submit data obtained from an additional 25 cases similarly treated to substantiate our thesis.

Surgical Treatment

The surgical technique of ovarian wedge resection for bilateral polycystic ovaries is as follows:

A Pfannenstiel incision is made and the enlarged ovaries are delivered into the operative field. Retractors may be removed and lap pads are not required in the peritoneal cavity. The ovaries are separately and successively held by means of a Scudder clamp covered with rubber tubing. A wedge is dissected from the ovary by sharp dissection, the size of which is determined by the amount of ovarian enlargement. The follicle cysts remaining in the ovary are punctured from within the ovarian incision, and tension is thus released. With No. 00 plain catgut, and a fine, full-curved, noncutting needle,

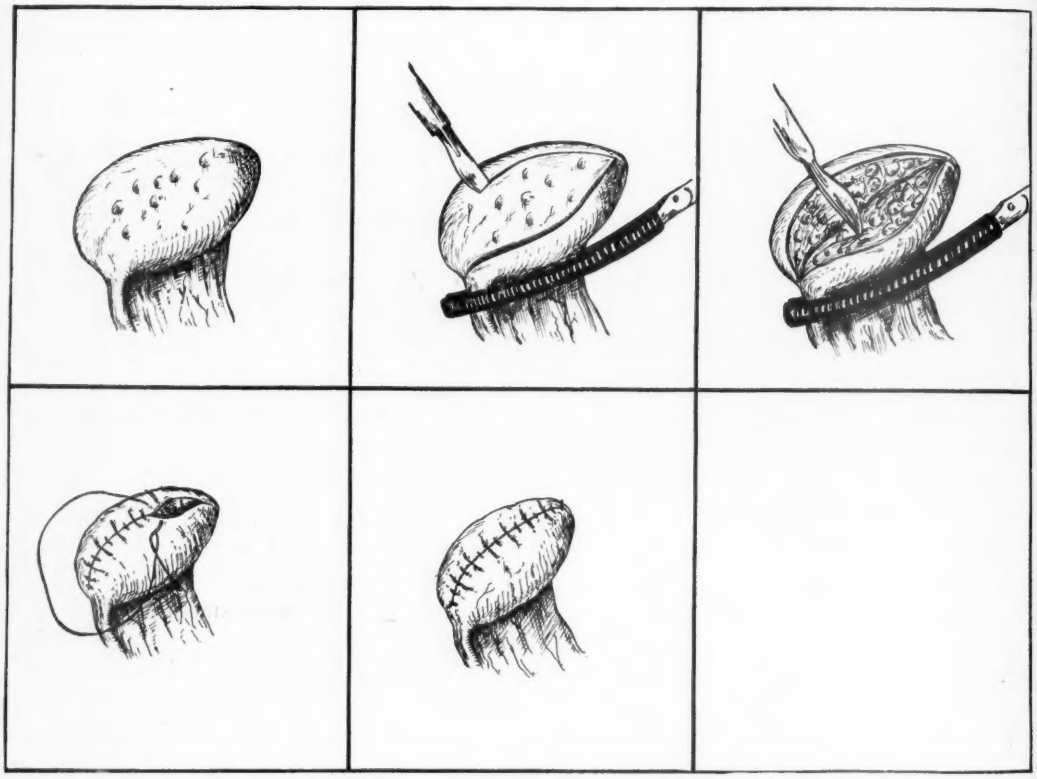

Fig. 8.—Technique of wedge resection of ovaries.

two rows of continuous sutures are used to close the wedge, the first row deep to the base of the wedge, locked at the end, and returned as a second superficial approximation suture (Fig. 8). This leaves a single line scar. The clamp is removed, care being taken that compression of the ovarian vessels by the clamp lasts no more than twenty minutes (usually less than ten minutes is sufficient). Should there be bleeding, additional interrupted sutures insure hemostasis. Recently, we have introduced 5 Gm. of powdered sulfanilamide into the pelvis before closure, and we place the omentum between the sutured ovaries and the intestines. Closure of the abdominal wound proceeds as usual. The entire operation requires between thirty and forty minutes.

Results of Surgical Treatment

We have observed that when the ovaries have been resected, the physiologic sex cycle is resumed. Ovulation, which had been absent for periods

varying from a few months to several years before resection, takes place periodically. This has been satisfactorily shown clinically by carefully kept calendar records and in some instances by vaginal spreads, endometrial biopsies, and most significantly, by the occurrence of pregnancies.

Follow-up pelvic examinations have been made routinely and all except five patients have been followed for long periods of time; some for as long as ten to fifteen years. Following resection, there was a notable improvement, showing feminizing effects upon the individual. The breasts developed markedly, especially in those young women with primary amenorrhea and in whom the breasts were formerly immature. The uterus, which often was found to be hypoplastic, increased measurably in size within six months following surgery. There was distinct improvement in the patients' mental attitude, from one of frustration and sometimes depression, to one of cheerfulness and buoyancy. The tendency to obesity and acne rapidly disappeared.

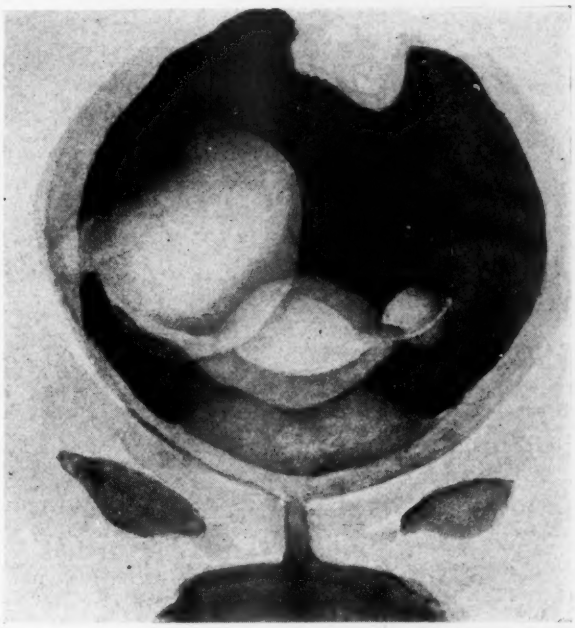

Fig. 9.—Asymmetrical involvement. Lutein cyst of right ovary one year after wedge resection.

The only sign to persist, more or less, was that of hirsutism. It was noted that after ovarian resection the hirsutism no longer increased in amount and distribution; in some instances, the hair on the abnormal sites appeared to lose its coarse texture and gradually become less evident. There was distinct evidence of feminization but no complete disappearance of the masculine hairy distribution which had already become a fixed pattern. It is our impression that this is the most persistent of the abnormal effects of bilateral polycystic ovaries.

As shown in the tables, there were no recurrences of typical bilateral polycystic ovaries in any patient treated by bilateral wedge resection. In one patient who complained of primary amenorrhea, menstruation was restored but it was irregular and later became excessive. She then complained of pelvic pain and it was found that a cyst had developed in one ovary (Fig. 9). A second laparotomy revealed an hemorrhagic corpus luteum cyst with adhesions to the omentum and bowel. In each of the other two girls, a simple cyst developed which required a second operation. In none of these, however, was there a recurrence of typical bilateral polycystic ovaries.

Summary and Conclusions

1. In the past fifteen years, we have studied 53 patients with bilateral polycystic ovaries.

2. These patients sought advice chiefly because of amenorrhea, sterility, and/or hirsutism.

3. The diagnosis of bilateral polycystic ovaries was usually based upon a typical clinical syndrome and was substantiated by demonstrating the ovarian lesions with gynecography (pneumoperitoneum).

4. Hormone and other medical therapy proved valueless in the treatment of this condition.

5. Surgical treatment in the form of bilateral ovarian wedge resection and suture of the ovaries has proved to be a satisfactory and most successful method of treatment.

6. Fifty-three patients were treated surgically. Seventeen married patients and three of the single patients who subsequently married (a total of 20)* became pregnant after operation (64.5 per cent), resulting in 26 pregnancies and 28 babies. This number was obtained as four women were pregnant twice, one three times, and there were two sets of twins.

7. Periodic checkup postoperatively revealed that there were no recurrences of bilateral polycystic ovaries. Three single women who had febrile and painful postoperative courses developed a unilateral ovarian cyst with adhesions (5 per cent).

8. On the basis of our study, we recommend that bilateral polycystic ovaries associated with amenorrhea, sterility, and/or hirsutism, be treated by bilateral ovarian wedge resection.

Since compilation of statistics for this paper, seven additional patients have been treated by bilateral ovarian wedge resection, bringing the total to 60.

I wish to acknowledge gratefully the assistance of Dr. Paul Steinhart, Miss Margaret Weis, R.N., and Miss Paula Bennett in preparing this report.

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Discussion

DR. EDWIN F. HIRSCH.—Realizing an hormonal imbalance of function in the glands of internal secretion in this disorder, notably the pituitary and the ovaries, Dr. Stein and his associates have studied the effects of wedge excisions of the ovaries, and have accumulated evidence to indicate that this operation does relieve the associated amenorrhea and sterility.

How this operation accomplishes the results obtained has interest. It apparently corrects a disarranged interrelated cycle of ovarian and pituitary glands. Since the changes of the ovarian tissues are in the direction of retrogression and atrophy, the complemental substance of the pituitary gland needed for the luteinization of the theca interna cells of the follicles and the further growth of the corpus luteum may not be stimulated to the functional level. Another possibility is that the effects on the follicle tissues of the ovary are in-

*Four additional pregnancies reported in this group since presenting this paper, and before publication, equals 24 patients pregnant, or 72.7 per cent.

effective because of local nutritional or fluid circulation factors. The edema of the stroma in these polycystic ovaries suggests that such a disturbance is present and that pressure effects are concerned, that may be relieved by the wedge resection of the ovaries. The tissue changes in the ovaries seem to move in a vicious circle. The more chronic the condition the less hope there is for functional recovery by surgical operation. Theoretically, the release of pressure within the ovaries may be beneficial because of an enhanced venous or lymph drainage or an increased arterial blood supply.

DR. RICHARD A. LIFVENDAHL.—All of us seeing the pictures presented by Dr. Stein will assume that we should be able to palpate ovaries that are as large as these. We wonder if it is necessary to visualize these ovaries before operating and whether there is any risk to the patient from pneumoperitoneum. Out of 28 cases from 1935 to 1939 Dr. Stein examined 17 patients who had enlarged ovaries on palpation. Out of the 28 there were four that were indefinite and six were negative to palpation but positive to x-ray examination. Another advantage to x-ray examination is that the x-ray will help to convince the patient that something should be done about polycystic ovaries.

Another question concerns the associated pathology. Dr. Stein reports that six of the cases had an additional lesion such as cystadenoma, granulosa-cell tumors, considerable fibrosis, etc. My experience has been the same. A fibroma and a dermoid no larger than a centimeter in diameter have been found in the ovaries I have examined.

DR. EDWARD ALLEN.—I remember particularly one case that I reported to this Society of amenorrhea of twenty-four years' duration in which we resected the ovaries and took out wedges. These ovaries were one-third normal size. Sections showed no evidence whatsoever of any ova, and yet within a month this patient menstruated and the uterus enlarged. Later, she married and I think she became pregnant, though I did not see her at that time. Her uterus is now five or six times the size it was at the time of operation. On the basis of that case and Dr. Stein's report I have resected seven ovaries bilaterally through the cul-de-sac. They were all grossly normal ovaries. Five pregnancies rather quickly followed although these patients had had all kinds of sterility treatment for from three to seven years without results. This raises the question in my mind whether the cysts are important or whether it is not a mechanical thing entirely. It may work on the same basis as dilatation of the cervix, obviously not because we enlarge the canal but just due to the mechanical effects which change the balance of the hormones affecting the pelvis.

DR. N. S. HEANEY.—It is interesting that in an article on polycystic disease of the ovary and its relationship to sterility, there should be 23 unmarried women from whom you could not expect to get proof of your results. If I were preparing a paper on sterility, one of the first requirements would be patients who could get pregnant. It makes it hard to evaluate your work to put in a group of unmarried women. It is striking, however, that in the 30 cases of married women, 26 pregnancies occurred, with 28 babies.

Years ago we resected polycystic ovaries for various reasons and I have given it up, but Dr. Stein's results certainly give one reason to ponder.

DR. STEIN (Closing).—Of the single women three later married and all had babies. The reason they were operated upon was because they had long periods of amenorrhea and polycystic ovaries. Many of these girls were nurses in training and were referred because of menstrual disturbances. In this group particularly, where vaginal examinations were not done in accordance with training school policy, we found the x-ray a very accurate method of diagnosis.

In answer to the question of danger in inducing pneumoperitoneum, we have employed gynecography for twenty years, and all the members of the hospital and clinic staff and many residents participated in it; we have never punctured a bowel or had a death from shock. I do not know why there has been the obvious lack of interest in the method outside of Michael Reese Hospital. However, if you go back twenty-five or thirty years, you will find that the men who studied tuberculosis were very much averse to using roentgenography because they feared injury to the chest. It took them a long time to be convinced that the x-ray was safe and would show something more than they could discover by other means. Resistance to new methods has been the same with every special group. Gynecography is one of the methods which has proved very valuable, particularly where there has been a difference of opinion. It has proved to be a safe and accurate method in our hands.

Dr. Lifvendahl asked about how many patients who were x-rayed did not show ovarian enlargement. I could not answer that question because we only reported those that did show enlargement and in whom the diagnosis was established. However, even when we palpated the ovaries, we used x-ray for corroboration. In some cases we had to use it as a diagnostic method because we could not palpate the ovaries. We used the x-ray either for corroboration of the diagnosis or where we had made only a presumptive diagnosis.

The associated lesions found in the ovary as a rule were described as microscopic, not macroscopic. It is true that in almost any ovary that you resect you will find little elements, small fibromas on the surface, or some other pathologic structure in the ovary.

I think Dr. Allen's procedure through the cul-de-sac is interesting. Dr. Zondek has punctured a number of bilateral polycystic ovaries through the cul-de-sac. In a former presentation I mentioned a method of splitting the ovary and turning out without sewing, and of decortication which was done in Cleveland by Reycraft. I think the best methods are the completely surgical techniques. There is more danger of adhesions when the incision is not accurately sutured.

MANAGEMENT OF PLACENTA PREVIA

A Twelve-Year Study

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THE purpose of this study is to analyze the results of our present methods of treatment of placenta previa and to indicate by what means we may achieve further improvement in the treatment of this serious obstetric complication. A review of the literature shows that there has been marked improvement in the fetal and maternal mortality figures for the treatment of this condition in the past twenty-five years. The use of cesarean section for placenta previa has been demonstrated to be one of the most important factors for this improvement. Prior to the use of this method, which is relatively modern, a maternal mortality rate of 10 per cent and fetal mortality from 50 to 60 per cent was considered satisfactory. Following the judicious use of cesarean section the fetal and maternal mortality rates were immediately reduced. Another important contribution to the improvement in results, particularly in lowering the maternal mortality rate, is the use of blood transfusion. A third factor which we would like to emphasize, that has been responsible for bettering the results, is the discarding of an old tradition in obstetrics, namely, that placenta previa patients must be delivered immediately.

Our present routine for the treatment of patients with vaginal bleeding in the last trimester of pregnancy is as follows: Following a routine vaginal preparation the patient is sent to the delivery floor for observation. Blood typing and cross-matching is carried out. Unless forced to do so earlier by continued profuse vaginal bleeding, the patient is taken to the operating room on the fourth day following admission, where a sterile vaginal examination is carried out. If central placenta previa is found, cesarean section is the treatment of choice, while in the marginal as well as in some of the partial cases an attempt is made to control the bleeding by simple rupture of the membranes. However, the treatment for all types may be influenced by the parity of the

patient, the duration of the pregnancy, the amount of bleeding, and the condition of the patient and the fetus. If the viability of the fetus is questionable, the cervix closed and firm, and there is little bleeding, the patient may be returned to the delivery floor where she may continue to be observed for a much longer period. It should be noted that at the time of examination the operating room has been prepared for immediate cesarean section or insertion of a hydrostatic bag, so that treatment may not be delayed should increased vaginal bleeding be encountered. If cesarean section is decided upon, the type of operation and the choice of anesthesia are dependent upon the preference of the operator.

This report is based on the study of 162 cases of placenta previa in which the diagnosis was made either by vaginal examination prior to delivery or by noting the placental location at the time of cesarean section. Since there were 40,862 cases delivered in the Woman's Clinic of New York Hospital during the twelve-year period of this study, the incidence of placenta previa in this series is 1 in 252.

Table I shows that there were 60 cases in the marginal group, 30 of the partial variety, and 65 central. There were 7 cases in which the type was not determined. Since 6 of the 7 were delivered by cesarean section, it probably indicates the difficulty which is often encountered in making an accurate diagnosis of the type of placenta previa at this time. There was one twin pregnancy in the group. Two patients were also diagnosed as having premature separations of the placenta at the time of admission. In both cases the separation of the placenta was extensive enough to result in the intrauterine death of the fetus prior to the onset of labor. In one patient the diagnosis of placenta previa was made in her second and third pregnancies which occurred four years apart. A low flap cesarean section under local anesthesia was performed on both occasions and each time the diagnosis of central placenta previa was made. There were two other patients who gave a history suggestive of a placenta previa in previous pregnancies which were delivered elsewhere. One of these patients had been induced at eight months because of vaginal bleeding, and in the other case a cesarean section had been performed for central placenta previa.

TABLE I

TYPE OF PLACENTA PREVIA	NUMBER OF CASES
Marginal	60
Partial	30
Central	65
Unclassified	7
Total	162

Table II shows only 161 cases as one patient died before delivery. It demonstrates that in the patients who were delivered, 50 had had no previous viable pregnancy, while 111 had had one or more such pregnancies. This figure is increased to 112 when the patient who died before delivery is included. It also shows that 84 patients were delivered vaginally and 77 by cesarean section. The figures are particularly interesting in the central placenta previa group where it is seen that only 12 of the 65 cases were delivered vaginally and of the 22 primiparas only one was delivered by this route.

TABLE II

	MARGINAL		PARTIAL		CENTRAL		UNCLASSIFIED		TOTAL	
	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.
Vaginal delivery	10	37	8	16	1	11	0	1	19	65
Cesarean section	5	8	4	1	21	32	1	5	31	46
Total	15	45	12	17	22	43	1	6	50	111
	60		29		65		7		161	

Table III shows the changes in the trend of treatment for the twelve-year period. The total number of cases for each year is listed, then the number of Voorhees' bag insertions, and the number delivered by cesarean section. The entire twelve-year period is then

divided into three separate periods to show the decreasing use of the hydrostatic bag and the increasing incidence of cesarean section. In the first period the bag was used in 44.1 per cent of the cases. This decreased to 26.8 per cent in the second period, then to 15.8 per cent in the last four years. The incidence of cesarean section on the contrary has changed from 30.9 per cent in the first period to 53.6 per cent in the next period, and finally to 68.4 per cent in the last four years. Of the total number of cases the Voorhees bag was used in 31.5 per cent, and 47.5 per cent were delivered by cesarean section.

TABLE III

YEAR	TOTAL	BAG	CESAREAN SECTION	PER CENT BAG	PER CENT CESAREAN SECTION
1932	5	2	0	44.1	30.9
1933	12	8	1		
1934	15	6	5		
1935	19	8	8		
1936	17	6	7		
1937	17	4	10	26.8	53.6
1938	13	3	8		
1939	12	5	4		
1940	14	3	8		
1941	11	2	9	15.8	68.4
1942	14	1	11		
1943	7	3	3		
1944	6	0	3		
Total	162	51	77	31.5	47.5

Table IV shows the average length of time spent in the hospital following delivery. Slightly less time was spent in the hospital by the group delivered spontaneously than by those who had been treated with the hydrostatic bag. This is due largely to the fact that the multiparas in this group had a much shorter convalescence. The chart also shows that the length of the hospital stay averaged six days more following cesarean section than for any other type of delivery.

TABLE IV

	SPONTANEOUS		HYDROSTATIC BAG		CESAREAN SECTION	
	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL
Primiparas	9	13.8	10	13.5	32	19.8
Multiparas	14	11.8	41	13.6	45	18.2
Total	23	12.6	51	13.6	77	18.9

In Table V the morbidity and average stay in the hospital for the various types of delivery is presented. Any patient having an elevation of temperature to 38° C. (100.4° F.) or over for any two days was considered to have morbidity. Any patient having an elevation in temperature to this level during labor was considered to have an intrapartum infection and even though there was no elevation in temperature following delivery, such a patient was classed as a morbidity. Using these criteria it is seen that there was a marked increase in the morbidity rate for the cesarean section group as might be expected for any laparotomy. The lowest morbidity rate was in those delivered spontaneously or by breech or forceps without prior use of the hydrostatic bag. In this group simple rupture of the membranes was sufficient to control the bleeding. Here the morbidity was 30.8 per cent as compared with a morbidity of over 50 per cent for the other types of vaginal delivery. The average stay in the hospital was 12.4 days, which is seen to be slightly less than for the other types of vaginal delivery.

TABLE V

TYPE OF DELIVERY	TOTAL CASES	MORBIDITY (NO.)	MORBIDITY (%)	AVERAGE STAY IN HOSPITAL
Bag with spontaneous breech or forceps	25	13	52.0	13.3
Bag with version and extraction	26	14	54.0	14.0
Version and extraction alone	7	4	57.1	13.4
Spontaneous breech or forceps	26	8	30.8	12.4
Cesarean section	77	55	71.4	18.9
Total	161	94	58.4	16.0

Table VI presents a study of the fetal mortality for the various types of delivery. Since in some cases the choice of the type of delivery would be altered if there was no chance of obtaining a living infant, it was deemed advisable to correct the figures in order to get a better picture of the results. Therefore, in the corrected figures, where there was no fetal heart heard on admission, where the infant was under 1,500 grams, and where there was a monstrosity or other disease in the infant, such as erythroblastosis fetalis, these cases were excluded. There was little change in the gross and corrected fetal mortality rates in the groups in which the hydrostatic bag was used. In the group delivered by version and extraction alone there was a gross mortality rate of 57.1 per cent and a corrected rate of 0. Since there were only 7 cases in the group it is probably too small to be of any real significance. In the group of 26 cases which were delivered either spontaneously or by breech or forceps without the prior use of the Voorhees bag, there was a change from 34.6 per cent to 11.5 per cent from the gross to the corrected mortality rates. This latter figure is almost the same as that obtained in the group of 77 patients who were delivered by cesarean section.

TABLE VI

TYPE OF DELIVERY	NUMBER OF CASES	TOTAL FETAL MORTALITY			
		GROSS		CORRECTED	
		(NO.)	(%)	(NO.)	(%)
Bag with spontaneous breech or forceps	25	12	48.0	10	40.0
Bag with version and extraction	26	11	42.3	9	34.6
Version and extraction alone	7	4	57.1	0	00.0
Spontaneous breech or forceps	26	9	34.6	3	11.5
Cesarean section	77	14	18.2	9	11.7
Total	161	50	31.1	31	19.3

Table VII presents an analysis of the two types of cesarean section that were used and the two types of anesthesia. It should be noted that one case was delivered by radical section, hence the total of the classical plus the low flap cesarean groups is 76 and not 77. The variations in the fetal mortality, morbidity, and average stay in the hospital for the four groups are so slight that it would be difficult to prove that the type of section or anesthesia were of any real significance.

TABLE VII

	NUMBER OF CASES	FETAL MORTALITY				MORBIDITY		
		TOTAL		CORRECTED		NUMBER OF CASES	PER CENT	AVERAGE STAY IN HOSPITAL
		(NO.)	(%)	(NO.)	(%)			
Classical cesarean section	46	10	21.7	6	13.0	34	73.9	20.2
Low flap cesarean section	30	4	13.3	3	10.0	21	70.0	17.1
Cesarean section with general anesthesia	52	8	15.4	6	11.5	38	73.1	19.7
Cesarean section with local anesthesia	25	6	24.0	3	12.0	17	68.0	17.2
Totals	77	14	18.2	9	11.7	55	71.4	18.9

In Table VIII it is seen that treatment was delayed four or more days following admission in 63, or 56.8 per cent, of the service cases, while among the private patients only 12, or 23.5 per cent, were treated in this way. This delayed method was used in 75, or 46.3 per cent, of the total number of cases. The longest interval between entry to the hospital and delivery was sixty-two days.

TABLE VIII

	NUMBER OF CASES	DELIVERED FOLLOWING FOUR DAYS OR LONGER	
		(NUMBER)	(PER CENT)
Private	51	12	25.5
Service	111	63	56.8
Total	162	75	46.3

We believe that there are two advantages in delaying the treatment of placenta previa cases wherever it is possible. In the first place any operative procedure is less hazardous if one allows the patient to recover completely from the initial shock, however slight this may

TABLE IX

TYPE	AGE	PARA	PERIOD OF GESTATION	CONDITION BEFORE TREATMENT	TREATMENT	TIME OF DEATH	COMPLICATIONS	REMARKS
Marginal	29	0	39	Excellent	Low flap cesarean section with general anesthesia. 500 c.c. transfusion postoperative	16th day	Febrile one day only. Pulmonary embolus	Pain and congestion in chest on 11th day with temperature 37.8° C. on 12th day
Central	29	ii	29	Excellent	Extraovular bag No. 3 four days before delivery. Braxton-Hicks version. Easy extraction	24th day	Pelvic thrombosis. Pulmonary embolus	Patient obese. Intrapartum infection. Afebrile puerperium. Discharged 12th day. Readmitted 17th day. Died 24th day
Partial	39	vi	33	Moderate shock	Intraovular bag No. 5, 500 c.c. transfusion	Undelivered	Temperature 39° C. on admission. Died 7 minutes after start of transfusion	May have been transfusion reaction
Marginal	32	iii	30	Slight painless bleeding. Dead fetus	Version and extraction. Manual removal of placenta. 1,000 c.c. transfusion	10th day	Macerated fetus 760 grams. Erythroblastosis. Patient Rh−. Donor's blood Rh+. Anuria	Hematin crystals demonstrated in kidney tubules at autopsy
Central	37	vii	39	Slight bleeding. Intrapartum infection. Temp. 38° C. Dead fetus	Version and extraction. Hysterectomy. 2,000 c.c. transfusion	7 hours post partum	Severe shock following delivery. Ruptured uterus	

be. Second, we believe that the chances of infection are diminished if this waiting period can be observed. It is therefore possible to have the advantages of an elective operation if cesarean section is decided upon.

There were 7 patients who developed phlebitic phenomena in the series, an incidence of 4.3 per cent. Five of these occurred following cesarean section, making an incidence of phlebitis of 6.5 per cent in this group. Three of the 7 patients had thrombophlebitis alone while the other 4 also had pulmonary emboli. Three of the cases were delivered by classical cesarean section and 2 by low flap cesarean section. One patient had local anesthesia and the other 4 had general anesthesia. Of the 2 patients who were delivered vaginally, one delivered by breech extraction following a Voorhees bag insertion and a Braxton-Hicks version; the other patient was delivered by craniotomy.

There were 5 maternal deaths in the series, making a mortality rate of 3.1 per cent. There was one death among the patients who were delivered by cesarean section, making a mortality rate of 1 to 77 cases, or 1.3 per cent. One patient died before delivery so that the death rate for the vaginal group was 3 in 84, or 3.6 per cent.

Table IX shows that two of the five deaths were due to pulmonary embolus. The first was a 29-year-old primipara with a marginal placenta previa who was delivered by a low flap cesarean section under general anesthesia. A 500 c.c. blood transfusion was given following operation. She died on the sixteenth day although she had been febrile only one day and had exhibited no symptoms of thrombophlebitis. The second patient had a central placenta previa. She was 29 years of age and had had two full-term pregnancies. She was delivered of a 1,510-gram stillborn infant by breech extraction following a Braxton-Hicks version. Four days before this a Voorhees bag had been inserted extraovularly. She had an intrapartum infection but the puerperium was afebrile and she was discharged from the hospital on the twelfth day. She was readmitted to the medical service on the seventeenth day with a diagnosis of pelvic thrombosis and pulmonary embolus. She died on the twenty-fourth day following delivery.

There were two deaths which occurred possibly as the result of a transfusion. One patient, who was 39 years of age and had had six full-term pregnancies, had a partial placenta previa at the time of insertion of a Voorhees bag intraovularly. She was in moderate shock, and a 500 c.c. transfusion was started at the end of the procedure. She died undelivered seven minutes after the start of the transfusion. There was no other obvious cause for her death. The other patient was 32 years of age and had had three viable infants. She was found to have a marginal placenta previa and was delivered of a 760-gram macerated fetus by version and extraction. The infant was later found to have erythroblastosis fetalis. Following delivery the mother was transfused for mild shock and died in anuria on the tenth day.

The last patient was 37 years old, para vii, with a central placenta previa. A version and extraction were performed, following which it was found that the uterus was ruptured. Immediate hysterectomy was performed and 2,000 c.c. of blood were given by transfusion. The patient succumbed to shock seven hours after delivery.

Summary

A study of 162 patients with placenta previa is presented. The delay in operative treatment for careful study of bleeding patients who probably have placenta previa is not only feasible, but wise. We have found an increase in the incidence of the use of cesarean section to be advantageous. The best results from vaginal delivery were obtained in those cases in which the bleeding could be controlled by simple rupture of the membranes and the fetus delivered either spontaneously, by forceps, or by breech extraction. However, each patient should be evaluated as to the method of delivery. While there was slight increase in the morbidity rate and an increase in the number of days the patient remained in the hospital following cesarean section, the fetal mortality was greatly improved and the delivery simplified by this procedure. The type of cesarean section and the choice of anesthesia seems to be of little importance. Further study toward prevention of phlebitis is important.

We wish to take this opportunity to thank Dr. Henricus J. Stender for the privilege of presenting this study.

Discussion

DR. BENJAMIN P. WATSON.—I personally have gone through the different phases in the treatment of this condition. In 1925, when I was in Edinburgh, Dr. Douglas Miller and I made a review of our cases of placenta previa and came to the very definite conclusion that there were only two ways of treating it: one, by doing nothing at all, or by simple rupture of the membranes in the marginal cases; and the other, by cesarean section in the cases of partial and central placenta previa where the patient was not in labor and where the cervix was firm and unretracted. Then I came to Sloane Hospital in 1926, the home of the Voorhees bag, and found that the bag treatment of placenta previa was the accepted method in the great majority of cases. I went along with that method, and for many years after I came here the Voorhees bag was used in most of our cases of placenta previa. Then last year we made a ten-year review of our cases of placenta previa which had been treated by simple rupture of the membranes, with the hydrostatic bag, and by cesarean section. From a review of that series we came to the same conclusions as those given us tonight, namely, that there are but two ways of treating the condition, simple rupture of the membranes or cesarean section.

I believe the hydrostatic bag belongs to a past era in obstetrics. It did a good job in the days when cesarean section was a hazardous operation, but I personally think that the Voorhees bag has a very limited place in the treatment of placenta previa in a modern obstetric service.

It might be of interest to mention the figures that we got in our ten-year study of placenta previa at the Sloane Hospital. We found, in contrasting cesarean section with bagging, in cases of central or of partial placenta previa, that the fetal mortality in our cesarean section cases was 4.1 per cent and in our bagging cases, 50 per cent; that the maternal mortality in cesarean section was 3.4 per cent and in bagging, 11.5 per cent; that the morbidity in bagging cases was 57.6 per cent and in cesarean section, 37.9 per cent; and as regards the patients who had lost a great deal of blood and were in profound shock, we found in cesarean section 16.3 per cent and in the bagging cases, 61.5 per cent. There was a lower fetal mortality, a lower maternal mortality, less shock, and less hemorrhage in the cesarean section cases than in those that had been bagged.

We also compared rupture of the membranes with bagging in cases of marginal placenta previa. These were the figures: the fetal mortality with simple rupture of the membranes was 16.6 per cent as against 25 per cent with bagging. We found that shock and hemorrhage occurred not at all in cases of simple rupture of the membranes, and that 62.5 per cent of the patients were shocked when bags were used.

So with these two comparisons of the severe types of placenta previa, bagging versus cesarean section, there was no question but that section had the better showing; and in the milder marginal placenta previa cases, rupture of the membranes versus bagging, simple rupture was superior.

DR. GEORGE H. RYDER.—To consider placenta previa as of one type only, is confusing and illogical, as the treatment and results vary so widely with the situation of the placenta, from the innocuous lateral type, through the dangerous marginal type, to the complete type—one of the most serious complications of pregnancy. Fortunately, over 60 per cent of previas are of the lateral type and probably not more than 6 per cent are of the complete type.

Dr. Watson has stated that there are only two methods of treating previas, rupturing of the membranes and section. This is practically true. But unless he explains that rupturing of the membranes is the treatment of lateral previa, and section of the complete, and serious forms of marginal previa, his statements will be misunderstood.

DR. SAMUEL A. COSGROVE.—Dr. Waters several years ago made a study of our bagging experience at the Margaret Hague Maternity Hospital which led to conclusions almost exactly like those of Dr. Watson. Dr. Williamson did not explain, to my understanding, the necessity of a four-day interval of observation, which I think he said was routine unless necessity required more prompt intervention. I think it is vastly important up to that point to do exactly what he described, no matter what the condition of the patient is when she is received; she is not touched until she has been typed and cross-matched. Blood or plasma is at hand and the operating room is completely set up for proceeding in any way indicated by the examination. Thus, with the patient on the operating room table, and with a full team in attendance, the vaginal examination is made to determine exactly the type of pathology present in terms that the speaker described. That having been determined, and the

management decided on, I see no reason for not proceeding to carry it out at once. That is our practice.

Our actual incidence of section in these cases is almost exactly comparable to Dr. Williamson's in his last period of observation, namely, about 65 per cent.

DR. HARVEY B. MATTHEWS.—There are three points that I would like to touch upon.

First, I would like to disagree somewhat with Dr. Watson regarding the use of the Voorhees bag in the management of placenta previa. I agree that rupture of the membranes and cesarean section are the two outstanding methods of treatment. On the other hand, there are certain cases of marginal placenta previa in multiparous women, where rupture of the membranes does not completely control the bleeding, and in those cases we still use the bag successfully. On the other hand, it is true, as time goes on and as the technique of cesarean section has been greatly improved, that "bags" are dwindling in their popularity. However, I still think that there are a few selected cases in which the bag can be used very successfully.

The second point was more or less covered by Dr. Cosgrove and that is that we have always believed and taught that, when the diagnosis is made, there is no expectant treatment of placenta previa. Of course, there may be an occasional exception to this sweeping statement.

Third, I agree with Dr. Ryder that we should differentiate between marginal, lateral, and central placenta previa. As soon as this is done, there is no reason for delay in choosing the method of procedure. We proceed to make the diagnosis by repeated cystograms. One cystogram, if positive, may be sufficient; but, if negative, it is not very helpful. Therefore we may do one, two, three, or more cystograms, if conditions warrant. Then, under proper surroundings, as has already been outlined, we do a vaginal examination in order to determine further the type of previa we are dealing with. Following these procedures, that is, having made the diagnosis of placenta previa and determined the type, the appropriate treatment is instituted. This may be simple rupture of the membranes, insertion of Voorhees' bag with or without vaginal pack, or cesarean section.

DR. RALPH L. BARRETT.—Time of treatment of the patient with premature separation of the placenta is of extreme importance.

If you see a patient for the first time late in labor with a partial dilation and an obliterated cervix, particularly in the multiparous patient, you may be able to handle the case successfully by delivery through the vaginal route. However, if the diagnosis is made early in labor or before labor and the cervix is not dilated and obliterated, I do not see how, in view of all that we have heard here tonight, that there can be the slightest question as to the proper method of treatment of placenta previa.

In my opinion, the proper method of treatment is delivery by the abdominal route when the patient is seen early and before the cervix has dilated and effaced with its incident hemorrhage.

DR. CLAUDE E. HEATON.—In 1934, Dr. J. P. Marr made a study of 146 cases of placenta previa treated at the New York Nursery and Child's Hospital, in which he came to practically the same conclusions we have had presented. Maternal mortality in delivery by the vaginal route was 5.6 per cent; in 40 cases treated by cesarean section the mortality was 2.5 per cent. The one death was due to transfusion reaction. The fetal mortality was 20 per cent in cesarean section and 49 per cent in vaginal delivery.

The mortality rate was just as high in those cases in which the placenta was situated in the least malignant situation as it was when the placenta was situated in the supposedly malignant site, centralis. In placenta previa the placenta is located in the lower uterine segment and death occurs from injury to this segment. Cesarean section is the operation of choice if one wishes to lessen the hazard for both mother and baby.

DR. ELIOT BISHOP.—The position of the placenta when implanted in the lower uterine segment should be considered from two points of view, the placenta and the cervical canal. At the risk of seeming to be too academic, I will give what I consider the proper nomenclature for each point of view. The placenta may be placed either centrally, laterally, or marginally, in relation to the cervical canal. From the point of view of the cervical canal the placenta previa may be either complete or partial. Examination usually shows only this viewpoint and not the placenta. I doubt that an x-ray cystogram will give us the differential.

Some deviations may occur from these academic viewpoints and nomenclature, such as velamentous insertion of the cord.

As to the treatment of placenta previa as such, I believe that everyone is in accord as to the proper planning and setup before even the examination is made. In the case of a primipara I will subscribe to the modern trend of using a cesarean section. If the patient is a multipara with living children, I think we cannot entirely discard the more conservative methods of vaginal attack. As the speaker and the previous discussers have stated, when the margin of the placenta is found, a simple rupture of the membranes will suffice. If it can be demonstrated that the placenta is presenting laterally and the cervix soft and dilated or easily dilatable, the Braxton-Hicks maneuver should be done.

However, this I do emphatically emphasize—after the foot is brought down there should *never* be *extraction.* A spontaneous delivery is obligatory. If we are committed to this procedure, the mother's and the child's life is our objective.

DR. GEORGE L. BOWEN.—In a study of placenta previa at Bellevue Hospital in 1938, Dr. Salter found that from 1922 to 1932, only 21 per cent of the patients with placenta previa received blood transfusions, and from 1932 to 1938, 50 per cent received them. This resulted in a decrease in the mortality from 11.5 per cent to 2.0 per cent. As Dr. Greeley has emphasized, there are other factors than just the method of delivery which have contributed to the lowering of the mortality rate.

DR. ARTHUR V. GREELEY (closing).—In answer to Dr. Cosgrove: it is difficult to prove the value of this waiting period. However, we feel that these patients are in better condition to withstand operative intervention at this time than they are at the time of admission when they have not recovered from the effects of the initial hemorrhage. We believe that our results were partly due to observing this waiting period.

SHOULD WE CHANGE OUR PRESENT STANDARD ON INFANT VIABILITY?

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THE birth of a premature infant invariably arouses interest and invites speculation as to what constitutes the lower limit of viability. Periodically, one encounters newspaper articles giving the impression that the particular infant reported is the smallest on record. In order to discover the smallest authentically recorded premature baby, and at the same time re-evaluate our concept of the lower limits of viability, the literature on the subject has been carefully reviewed, and three cases of very premature infants from our own hospital are here recorded. The subject should be of special interest to those doing obstetrics, since upon the accoucheur commonly falls the responsibility for the immediate postnatal care so all-important for the survival of these tiny infants.

Various criteria are used to determine whether a fetus is viable. Thus, on the basis of the duration of pregnancy, a fetus which has remained in utero twenty-six to twenty-eight weeks is generally said to be viable.[11-13] In terms of body length, this corresponds to about 35 or 36 centimeters.[14] Still another standard is that set by law, which varies among the states but usually requires birth and death certificates for an infant when the duration of gestation is five months or more (Table I). This is in accord with the Model Vital Statistics Act of 1941. However, sixteen states and the District of Columbia have other legal limits, varying from that of Maryland (any recognizable product of conception) to those of Washington and Indiana (seven months or over). A point which should be obvious, yet bears

TABLE I. PERIOD OF GESTATION AT WHICH REPORTING OF STILLBIRTHS IS REQUIRED

STATE	MINIMUM PERIOD OF GESTATION
	Agrees With Model Vital Statistics Act, 1941
Alabama	Advanced to 5th month
Arizona	Advanced to 5th month
Arkansas	5th month
California	Advanced to 5th month
Colorado	5 months (20 weeks) or more
Delaware	5 months
Florida	Advanced to 5th month
Georgia	Advanced to 5th month
Illinois	Advanced to 5th month
Iowa	Advanced to 5th month
Kansas	Passed 20th week
Louisiana	5 months (20 weeks) or more
Maine	5 months or more
Michigan	Advanced to 5th month
Minnesota	Advanced to 5th month
Mississippi	5 months
Missouri	5 months
Nebraska	Advanced to 5th month
Nevada	After at least 20 weeks
North Carolina	Advanced to 5th month
North Dakota	5 months
Oklahoma	Advanced to 5th month
Oregon	After at least 20 weeks
South Dakota	Advanced to 5th month
Tennessee	5 or more months
Texas	Advanced to 5th month
Utah	Advanced to 5th month
Vermont	5 months or over
Virginia	5 months (20 weeks) or more
West Virginia	Advanced to 5th month
Wisconsin	5th month
Wyoming	After at least 20 weeks
	Less Than 20 Weeks
Maryland	Any recognizable product
New York*	New York City—every product of conception
Ohio	At least 4½ months
Pennsylvania	4 months
	More Than 20 Weeks
Connecticut	After not less than 28 weeks
District of Columbia	Passed 5th month
Idaho	Development sufficient to give chance of life
Indiana	7 months and over
Kentucky	5½ months
Massachusetts	After 5 months
Montana	6 months or 24 weeks
New Hampshire	28 weeks
New Jersey	Advanced beyond 5th month
New Mexico	5½ months
Rhode Island	6 completed months
South Carolina	22 weeks
Washington	Advanced beyond 7th month

*The law for New York State (exclusive of New York City) is in accord with the Model Vital Statistics Act.

emphasis, is that such criteria do not make survival impossible for infants who fail to measure up to them. Every effort should be made to save even those babies which appear nonviable by these standards.

It is accepted that the prognosis for survival of an infant varies with its weight. Those weighing less than 1,000 grams (2 pounds, 3 ounces) naturally do not have a very good outlook, yet a survey of the literature (Table II) shows that at least 54 such cases are on record. It is interesting to note that the smallest surviving infant had a minimum recorded weight of 420 grams (Monro[7]).

In 1941 two infants with minimum weights of less than 1,000 grams were born in the Maternity Division of the University of Michigan Hospital. Both were born of mothers with chronic nephritis. The pregnancies were interrupted artificially at about 6 to 6½ months of gestation, and the deliveries were spontaneous. The smaller infant weighed 705 grams (1 pound, 9 ounces) and the other 934 grams (2 pounds, 1 ounce) when first weighed on their

TABLE II. REPORTED CASES OF SURVIVING INFANTS WEIGHING LESS THAN 1,000 GRAMS

YEAR OF REPORT	REPORTED BY		MINIMUM WEIGHT RECORDED (GRAMS)	BIRTH WEIGHT	SEX
1922	Huber, O.		790		F
	Oberwarth	1921	500		
	Hess	1911	690		
	Hess	1911	740		
	Oberwarth	1911	750		
	d'Outrepont		750		
	Meyer	1912	750		
	Roth	1913	750		
	Heller	1912	800		
	Heller	1912	840		
	Ylppo		840		
	Frankenthal		850		
	Pfanndler	1907	860		
1922	Waegele	1917	860		
Hess	Klinker	1903	895		
Collection	Ahlfeld	1903	900		
	Pizzini	1908	900		
	Jardine	1902	907		
	Villemain	1895	950		
	Maygrier and Schwab	1907	970		
	Heiberg		975		
	Rommel		980		
	Ahlfeld	1903	980		
	Tissier	1912	990		
1928	Pulford & Blevins			680	F
1930	Schoedel		720	800	M
			960	1,000	F
				950	M
				970	F
			980		F
1931	Fischer-Ban		540	600	
1931	Temesnary		600		
1933	Houlihan		666	705	M
			745	900	F
			840		F
			850	940	M
1934	Kunstadter and Bartelme		850	890	F
			905	995	F
(Collection			850		F
1922-1934)			940		M
			865		M
			890		F
			790		F
			970		F
			755	825	M
			890	1,005	M
			945	1,075	F
			970	1,075	F
			990	1,075	F
			945	1,060	F
			925	1,050	F
1936	Stander			928	
1938	Hoffman, Greenhill & Lundeen		595	735	F
1939	Monro		420		M
1945	Haas (present article)		705		M
			830		M
			934		M

ninth and sixteenth days, respectively. Both babies were cared for by the regular nursing staff, and were kept in incubators with continuous oxygen for nearly two months. Inhalations of 5 per cent carbon dioxide were used frequently during the first few weeks.

The third infant, born in 1944, weighed 830 grams (1 pound, 13 ounces) when first weighed, 16 days after birth. The circumstances surrounding the birth of this child were somewhat different than for the two preceding cases. The mother had intermittently threatened to abort from the third month until the sixth, when the membranes ruptured spon-

taneously, and labor ensued two weeks later. The baby was born spontaneously as a frank breech presentation. The placenta was incarcerated and required manual removal.

The care of all three infants was essentially the same. For several hours after birth nothing was given by mouth, and great care was taken to see that aspirated mucus and amniotic fluid were suctioned off as necessary. When respirations were well established (18 hours in the first two, and 48 hours in the last case), feedings of 5 per cent glucose water were offered in ¼ ounce quantities every two hours until it was well taken, at which time a formula was substituted.

In the absence of available breast milk, feedings consisted of an evaporated milk, corn syrup, and water formula. This was at first quite dilute, but was rapidly concentrated to give about 20 calories per ounce of formula. Occasionally, protein milk was added to increase the caloric value. The amount of each feeding was determined by the infant's appetite, starting with ¼ ounce and increasing as tolerated. It was interesting to note that under this plan the infants took enough formula to provide 65 to 80 calories per pound of body weight per day, this figure dropping gradually as the weight increased.

The sucking reflex was fairly well developed in all these babies. They were fed at first by means of a medicine dropper with a short piece of rubber tubing over the end for a mouthpiece. This was followed as tolerated by a Breck feeder, and finally by a regular nursing bottle. It should be emphasized here that the first feedings with the Breck feeder should be given by a nurse experienced in feeding babies. Otherwise, aspiration of formula with disastrous results is likely to occur. The administration of vitamins A, C, and D, and iron (elixir of ferrous sulfate) was begun in all cases as soon as the formula was being well taken. At no time was it necessary to resort to tube feeding. Subcutaneous fluids were used only rarely. Because of the infant's susceptibility to infection and because of the greater amount of handling required, it is our policy to avoid the use of parenteral fluids whenever possible.

Follow-up has been obtained in each of the earlier cases. The smaller infant (J. M., No. 492130) is now over 3 years old. He stood alone at 18 months and began walking at 23 months. When 2 years old he had 16 teeth and weighed 24 pounds. His mother reports that he is the most active of her five children, eats anything offered, and has had no illnesses except a slight cold when about 14 months old.

The second child (G. F., No. 496857) has not been so fortunate. At the age of 6 months he was returned to the hospital as a feeding problem with rumination. It was also found that he had thrush, ocular nystagmus, and retinal hemorrhages. It was felt that the prognosis for good vision was very poor. Under management by members of the Pediatrics Department the feeding problem was readily corrected, and on subsequent checkup at the age of 9 months he seemed to be progressing satisfactorily. It is now reported that he weighed 18 pounds at 1 year, and at 23 months weighed 25 pounds. He started to crawl at 13 months and took his first steps at 19 months. Sixteen teeth have erupted. His mother reports that she thinks vision of the left eye is poor but is "real good" in the other eye. He speaks several words, and seems very active and healthy now.

The third infant weighed over 6 pounds when discharged from the Hospital at a little over 3 months of age.

While excessive handling and unnecessary weighing are to be scrupulously avoided in caring for premature infants, the frequently reported *birth* weights of prematures indicates that curiosity often overbalances judgment. The infant should be placed in an incubator at once and the first weighing delayed until his condition warrants, whether this be one or several weeks later.

One often encounters the contention that the prospects for satisfactory mental and physical development of very small premature infants do not justify the prolonged and tedious care which they require. This problem has received considerable attention and study, and it has been quite definitely shown by Hess, Mohr, and Bartelme[8] that, excluding cases with birth injuries, premature infants show development comparable to that of normal children. Physical growth in early years tends to lag somewhat behind that of term infants. Hess[10] reports similar findings.

The economic phase of this problem should also be considered. The great amount of special care and equipment necessary to raise a premature infant generally involves considerable expense. Again, the question may be asked, are

they worth it? If we use for comparison the care of patients afflicted with tuberculosis or malignant disease in which the outlook is often poor indeed, then the answer must be in the affirmative.

When hospitals can be equipped and staffed as we now feel they should be, the care of prematures will become more routine and less formidable, although some degree of special care and individualization will always be required.

In recent years certain developments have appeared which may be expected to improve the survival chances for premature infants. Among these may be mentioned new and improved incubators and other nursery equipment, which are becoming more readily available to all who need them; caudal anesthesia, which avoids excessive sedation and minimizes trauma to the delicate fetal head by relaxing the structures about the birth canal; and the Rh factor, knowledge of which may save many premature infants with hemolytic anemia of the newborn, through the use of proper transfusions. As a result of these advancements, it is likely that the number of prematures born alive will rise, thus increasing the importance of the question under discussion.

Discussion

To designate a given weight as the lower limit of viability can have no particular virtue except for statistical purposes. It can, however, engender the attitude and belief that no infant weighing less than such a standard can survive and therefore does not merit detailed attention. It is clear that although a given viability standard may be important to the public health statistician, it may actually be a handicap to the physician. Because of this and the evidence presented, it is obvious that the advantages are all in having the limit too low rather than too high. If there must be a standard, let it be based on recorded survivals. It is suggested that 1,000 grams (2 pounds, 3 ounces) would be a reasonable weight limit.

The number of recorded infants weighing less than 1,000 grams who have survived is not great, yet there are enough to show that every infant, no matter how premature, deserves full attention and opportunity for life. Some will survive, and most of the survivals will develop into worth-while individuals.

Summary

1. The literature on the survival of premature infants with minimum weights of less than 1,000 grams has been reviewed and 54 cases found.

2. Three additional cases are reported.

3. Some recent developments which improve the survival rate for premature infants have been mentioned.

4. In the absence of available breast milk, properly adjusted artificial formula feedings have been found a satisfactory substitute.

5. It is pointed out that with increasing awareness of the possibilities of survival, and with greater effort, infants previously considered nonviable will survive.

6. One thousand grams (2 pounds, 3 ounces) is proposed as a lower weight limit of viability for statistical purposes.

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THE TREATMENT OF PRIMARY DYSMENORRHEA WITH DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX*)

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DYSMENORRHEA has been classified arbitrarily in two categories, primary and secondary. The latter usually appears during the third decade of life or later, and, in the majority of patients, fairly well defined pelvic pathology can be demonstrated. Careful study will usually reveal the presence of ovarian or uterine neoplasm, oophoritis, salpingitis, endometriosis, or some other tangible clinical entity which can be treated with directness and frequently with success. Primary dysmenorrhea, to which this discussion will be confined, commonly appears at or shortly after the menarche and is encountered, therefore, in young women who are usually nulliparous or virginal. Childbearing, although apparently helpful in many instances, will not guarantee complete or even partial relief from dysmenorrhea after the postpartum period. Menstruation usually occurs at regular intervals in these young women and the rate and amount of flow approximate the normal. Pelvic structure is within the normal range and, as a general rule, no pathologic conditions are demonstrable.

The treatment of primary or functional or essential dysmenorrhea has been most unsatisfactory for both clinician and patient because the etiology of the condition as yet is unknown. Many theories have been advanced and as many methods of treatment have been developed.

One of the oldest theories suggested that dysmenorrhea occurred in those individuals with certain structural defects such as stenosis of the cervix, anteversion or retroversion of the uterus, complete or partial infantilism of the genital tract, and a variety of other defects of greater or less importance. Corrective measures sometimes afford permanent or temporary relief, but since such procedures require a considerable degree of patient-physician cooperation or demand surgical intervention, they are not practicable under all circumstances. Furthermore, it is now rather widely accepted that the incidence and severity of structural defects are no greater in women who suffer with dysmenorrhea than in those who are not so afflicted.

*Depropanex is the proprietary name of deproteinated pancreatic extract prepared by Sharp & Dohme, Philadelphia, Pa.

Some aberration of the pelvic autonomic nervous system is sometimes thought to be responsible for the collective phenomena of dysmenorrhea. Attempted correction of such aberration is usually reserved for extreme cases and as a last resort. Even when careful technique is employed, however, surgical intervention is by no means always successful.

It is held by some that psychogenic factors are of major importance in women with dysmenorrhea. This is undoubtedly true in certain instances but by far the majority of dysmenorrheic women are emotionally stable and reveal no greater tendency toward neuroses or psychoses than do other individuals. It is also entirely possible that dysmenorrhea might precipitate or exaggerate a psychopathologic personality rather than the reverse.

During the past few years, a number of endocrine substances have been employed in an attempt to relieve or eliminate dysmenorrhea. Estrogens have little or no effect according to Winther,[1] but the results of other investigators[2, 3] indicate that these substances are capable of affording relief. Prolonged administration of the estrogens is necessary and the desired effect is attained by the induction of an anovulatory cycle. Lyon[4] has had favorable results with ethinyl estradiol, but oral medication must begin on the fifth day of the cycle and continue for twenty-one days. Relief from dysmenorrhea is afforded by the prevention of ovulation, which may not be desirable even temporarily in many instances, and certainly, as Lyon[4] states, "prolonged ovarian rest or follicle-stimulating hormone suppression has not been shown to be desirable." Laboratory and clinical evaluation have failed to produce evidence in favor of progesterone.[5-7] Androgens have also been used in an effort to reduce uterine bleeding or rather to "prevent relative pelvic vascular engorgement with its attendant effects on the pelvic sympathetic nervous system."[8] When androgens are employed, care must be taken to avoid possible atrophy of the endometrium which, of course, is most undesirable in women of the age-group in which primary dysmenorrhea occurs. Atrophy can probably be avoided by administering the small doses recommended by Cinberg,[8] but frequent subcutaneous injections are necessitated by such a procedure which greatly restricts its applicability.

Billig[9] has introduced a new method recently for relief from dysmenorrhea which is based upon the premise that in dysmenorrheic women "a postural defect of contracted ligamentous bands restricting the normal range of spinal-pelvic-femoral postural excursion is found present." The ligamentous contractures cause compression of nerve pathways which produces irritation to certain peripheral nerves. "This irritation gives rise to painful symptoms in the region of the distribution of these nerves and is proposed as the mechanics involved in producing symptoms of dysmenorrhea." Specific exercises are recommended for correction of this condition. The exercises are to be practiced three times daily and it is claimed that relief is afforded in from one to three months. Close supervision is required in order to direct proper execution of the special exercises. Such a regimen does not appear practicable for industry nor for many patients encountered in general practice, although good results are claimed by Dick, Billig, and Macy.[10]

Bickers[11] confirmed the work of Wilson and Kurzrok[12] on the normal human uterus, and later[13] demonstrated the difference between the painful and nonpainful menstruating uterus by kymographic tracings of uterine contractions prior to and during menstruation. Bickers believes that there is a congenital physiologic defect in the myomentrium causing the latter to react abnormally to the stimulus, which induces increased motility at the beginning of menstruation. The muscle is thrown into spasm and fails to relax between contractions. The absence of relaxation between contractions produces fatigue and "interferes with the normal oxygenation and nutrition of the myometrium. Muscle contraction in the presence of anoxia is associated with pain,"[13] and the symptoms of dysmenorrhea result. Bickers observed the effects of a number of drugs and endocrine substances when administered to normal and dysmenorrheic patients, but none were shown to have any favorable effect on uterine contractions with the exception of a nonnarcotic spasmolytic compound. It is interesting to note that this compound has papaverine-like properties and exerts its activity directly on the smooth muscle fiber itself. Unfortunately, the favorable effect of this drug was noted in only about one-third of patients when administered orally.

In a review of the literature concerned with essential dysmenorrhea Fremont-Smith[14] concludes that "the pain of dysmenorrhea does not occur in the absence of active uterine

contractions; and one or more secondary factors must be present if pain is to occur. If this is true, treatment of the disorder could be effective either by causing diminution of uterine contraction or by influencing this unknown secondary factor. One may regard the contraction as the precipitating and some other endocrine or circulatory factor as the predisposing cause of dysmenorrhea.''

With these facts in mind and with some experience in the use of most of the methods presently discussed, an attempt was made to discover a preparation which was nontoxic, which would produce the desired effect rapidly and with reasonable certainty in the majority of patients. The conclusion of Fremont-Smith appeared reasonable, and since the secondary factor was not known, a search was made for a substance which would diminish the contractions of the menstruating uterus. A review of the literature revealed that a suitable preparation was available which had an extensive clinical background but was employed almost exclusively in the fields of peripheral vascular disease[15-20] and in urology.[21-24] These reports indicate that the preparation is nontoxic and that it affects a relaxation of spastic smooth muscle.

Depropanex is a saline solution of a chemically derived, protein-free nitrogenous fraction obtained from an acid-alcohol treatment of beef pancreas. It is free of insulin, histamine, and acetylcholine, and contains approximately 2.5 per cent solids, including 0.5 per cent nonprotein nitrogen, 0.9 per cent sodium chloride, and 0.25 per cent phenol, as a preservative. The pH of the solution is adjusted to 6.5—6.8. The dose recommended in the current literature which describes clinical experience with this pancreatic tissue extract is from 2 to 5 c.c., administered intramuscularly.

Inasmuch as the stimulus for such an investigation emanated in part from a desire to reduce absenteeism in the industrial plants with which the author was associated on a part-time basis, it was decided to conduct this study in two plants, the personnel of which included a large number of women. The nurses at each of these plants were instructed, therefore, to administer depropanex intramuscularly to all employees who presented themselves for relief of dysmenorrhea. Since there was little or no information with regard to dosage in the treatment of this condition, it was considered advisable to begin with less than the minimal dose recommended for the more serious circulatory and urologic disorders described in the literature. Standing orders were written for 1.5 c.c. of depropanex to be administered intramuscularly. After the injection, provision was made for the patient to rest for a short period before returning to work or, if relief was not obtained, to be discharged to her home with the usual recommendations for palliative treatment. The same regimen was adopted for those patients seen in private practice. In some instances the dose was increased up to 4 c.c., but for the majority of patients 1.5 c.c. of the extract appeared to be sufficient.

It soon became evident that a number of factors were to be considered in the industrial study which did not appear in the investigation as conducted among private patients. There was a large labor turnover in the industrial plants and consequently it was frequently impossible to do follow-up studies or to repeat the medication in larger doses. Some employees, having been accustomed to oral medication and in many instances fully expecting to be excused from work because of the severity or alleged severity of symptoms, resisted parenteral treatment. It is interesting to note that in both plants when the pancreatic tissue extract was first used the majority of employees to whom

it was administered voluntarily extended favorable comments. These subjective observations were borne out by improved clinical appearance and the ability of the patient to return to work. Later, however, a number of vague and indefinite objections were raised in order to avoid the administration of the preparation. In a few instances in which such remonstrance was assuaged by the nurses, the patients denied any beneficial effect after the extract was administered. In most cases, however, such denial was not substantiated by the clinical appearance, since the general tension and the characteristic appearance of the facies had subsided markedly or had disappeared completely. Inasmuch as the symptoms of dysmenorrhea are almost entirely subjective, however, these employees were permitted to leave the plant, ostensibly to seek relief at home.

The experience among patients treated in private practice was quite different, and definite uniformly successful results were obtained in almost every instance. The degree of relief varied somewhat in different individuals, but in no case did the patient state that no relief whatever had been obtained after administration of the extract. It must be admitted, of course, that the patients seen in private practice were studied much more carefully than those in industry and that there was no doubt that the patients in the former category were properly classified with regard to the type of dysmenorrhea with which they were suffering, i.e., primary or essential dysmenorrhea. The majority of patients seen in private practice and included in this series had received a variety of therapeutic agents, including parenteral injections for relief from the symptoms of dysmenorrhea. Although some of these agents had afforded sufficient relief for the patient to resume her usual activity, none produced so marked an effect with such consistency as did pancreatic tissue extract. Relief in some instances has been so marked and has occurred with such relative rapidity that the patients so affected felt that a narcotic had been employed except for the fact that they experienced no drowsiness or other side effects which commonly result from such treatment. A noticeable decrease in pain occurs in most instances within fifteen minutes after administration of depropanex. In some patients the pain has almost completely disappeared within this time. In other individuals relief is more gradual and thirty minutes to one hour is required for amelioration or disappearance of symptoms. A few patients have noted that after several treatments the symptoms of dysmenorrhea have diminished to such an extent or have disappeared entirely so that further treatment has become unnecessary.

The history of one patient, perhaps, deserves special mention. She was 20 years of age and had had severe dysmenorrhea since the onset of the menarche at 14 years of age. She was unmarried, had had no pregnancies, and had been incapacitated for from one to three days consistently throughout her menstrual life. Hospitalization and thorough study on several occasions have failed to elicit any tangible cause for dysmenorrhea of such severe type. Depropanex was administered on two occasions in amounts of 2 and 4 c.c., respectively, with no favorable results. During the course of the next month a presacral neurectomy was performed and the subsequent menstrual period, which occurred shortly after partial recovery from the operative procedure, was quite painful and no improvement was noted as compared with the dysmenorrhea experienced before operation. After the pain had continued with no evidence of abatement for four hours, 2 c.c. of depropanex were administered intramuscularly. Partial relief was obtained in fifteen minutes and almost complete relief within one hour. The same experience was observed on three subsequent occasions. At this writing it appears that the symptoms are gradually diminishing in severity. During the last menstrual period no medication was administered and, although

moderate pain was experienced, the patient was by no means totally incapacitated as previously.

Table I shows the number of patients in each group, the number of treatments administered, and the number and percentage of treatments which resulted in complete and partial relief or in which no relief was obtained. Included in the latter group are those patients treated in industry who denied favorable response but whose clinical appearance, according to the observation of the attending nurse, was definitely improved. The marked disparity between the results obtained in industry and those obtained in patients encountered in private practice is most striking. In addition to the reasons outlined above which contributed to this wide difference, it is believed that closer medical supervision, such as that which can be maintained by a full-time industrial physician, would probably result in more favorable response to this method of treatment in industry and it would be possible to approximate the results obtained in private practice.

TABLE I. SHOWING THE NUMBER OF PATIENTS IN EACH GROUP, THE NUMBER OF TREATMENTS, AND THE NUMBER AND PER CENT OF RESULTS OBSERVED

CLASSIFICATION OF PATIENTS	NUMBER OF PATIENTS	NUMBER OF TREATMENTS	CLINICAL RESULTS					
			COMPLETE RELIEF		PARTIAL RELIEF		NO RELIEF	
			NO.	%	NO.	%	NO.	%
Private	25	63	50	79.4	11	17.5	2*	3.1
Industrial	31	41	22	53.7	6	14.6	13	31.7
Total	56	104	72	69.3	17	16.3	15	14.4

*These treatments were those administered to Miss G. W., whose case history is outlined above, prior to operative intervention.

No attempt was made during the course of this investigation to extend additional contributions concerning the etiology of primary dysmenorrhea. On the basis of the already accumulated knowledge, which is admittedly incomplete, an attempt was made to discover some preparation capable of producing a satisfactory clinical result. The favorable results obtained in this study and, particularly, the consistent success attained in a group of patients under close supervision indicate that the nontoxic, spasmolytic pancreatic tissue extract, depropanex, is a most valuable agent for relief of patients with dysmenorrhea and merits the attention of the profession for more extensive clinical evaluation.

Summary and Conclusions

1. A review of the literature reveals that no therapeutic agent has been available to the clinician which will afford consistently favorable results in the treatment of dysmenorrhea.

2. Recent laboratory and clinical investigation have clarified, to some extent, some of the factors involved in the production of dysmenorrhea and have indicated that the latter occurs only in the presence of active uterine contractions and that these contractions are spastic in character.

3. The effect of a nontoxic, spasmolytic agent, depropanex, which is a deproteinated pancreatic extract, was studied when administered to two groups of patients.

4. Uniformly consistent and favorable results were observed in the group of patients encountered in private practice who presented themselves for treatment for moderately severe, and severe dysmenorrhea. Twenty-five patients in this group received sixty-three treatments consisting of from 1.5 c.c. to 4 c.c.

of depropanex intramuscularly. Complete relief from dysmenorrhea was afforded within from fifteen minutes to one hour subsequent to the administration of fifty treatments (79.4 per cent). Partial relief was afforded within the same period of time after eleven treatments (17.5 per cent). Complete or partial relief, therefore, was obtained in twenty-five patients on sixty-one occasions which represent 96.9 per cent of treatments administered to this group.

5. Thirty-one patients included in the industrial group received forty-one treatments, twenty-two, or 53.7 per cent, of which afforded complete relief, and six, or 14.6 per cent, afforded partial relief from dysmenorrhea. Favorable response was denied after thirteen treatments (31.7 per cent).

6. The striking disparity of results obtained in the two groups are reasonably accounted for, and it is believed that if the factors mentioned were corrected, the experience in the industrial group would approximate that attained in the series of patients over whom closer supervision was maintained.

7. The results of this investigation indicate that deproteinated pancreatic extract is very effective when administered to patients with dysmenorrhea, and that favorable response is probably due to the spasmolytic action of depropanex on the uterine muscle.

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DIETHYLSTILBESTROL IN THE TREATMENT OF FUNCTIONAL OVARIAN DISORDERS

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IT HAS been customary to consider the various functional disorders of the human ovary as distinct clinical entities. There are many articles in the literature on the causes, associated symptoms, and treatment of amenorrhea; other articles on menorrhagia; and others on hypomenorrhea, infertility, cystic ovaries, and dysmenorrhea. Each disorder has been attacked separately with different treatment for each. Surgery has offered the most hope for many of these conditions, because of the unsatisfactory results from endocrine therapy.

Efforts to stimulate the ovaries have been largely unsuccessful. Hypophyseal (pituitary) gonadotropes and chorionic gonadotropes have been used singly and together. Mild roentgen-ray exposure of the ovaries and pituitary gland has been successful in some hands, but is not favored because of its inherent danger. As a result of the difficulty in stimulating the ovaries, substitutive glandular therapy has been used frequently, in the hope that a normal cycle would somehow be established.

Hamblen[3] used estrogens in menorrhagia in 1931. Karnaky[4] in 1940 advocated the use of diethylstilbestrol, a potent estrogenic hormone, for this condition which nearly everyone agrees is caused by an excess of estrin in the body. His argument was that the primary cause of the excess estrin is an unruptured Graafian follicle in the ovary. The ovum does not escape and an anovulatory cycle results. The estrin-containing liquor folliculi continues to be absorbed, and the corpus luteum forms poorly, if at all. Lack of progesterone from the corpus luteum permits the action of the estrin to go unopposed, so that the proper balance between these two hormones is disturbed. Thickened endometrium and excessive menstrual bleeding occur because of the hormonal imbalance.

Karnaky proposed to re-establish this balance, not by "neutralizing" the estrin with progesterone or androsterone in the classical manner, but by destroying the cysts in the ovaries through the use of large doses of diethylstilbestrol. The suggested dose, 5 mg. daily for twenty days, depresses action of the pituitary gland. It is believed that the unruptured Graafian follicle is resorbed, because of lack of prolan stimulation from the pituitary. The sudden withdrawal of the diethylstilbestrol at the end of the twenty days allows the action of the pituitary to resurge rapidly. This may produce an unusual stimulation of the ovary naturally.

On the basis of the foregoing theory, it was decided to give diethylstilbestrol in 5 mg. doses to any patient who had any of the so-called functional ovarian disturbances. These disturbances were interpreted to include dysmenorrhea, simple cystic ovaries (the "medical cysts" of Crossen[1]), irregularity in menstrual rhythm, menorrhagia, and infertility.

Material

This study has been given impetus by the fact that the women seen in the Army clinics are in the younger age group, in which the disorders of ovarian function are most

frequent. One hundred seven women were studied, all of whom had sufficient complaint to seek medical care for their pelvic disorders. Thirty-one had a single complaint and 76 had two to four of the functional ovarian disturbances. Of these 76, 38 had two complaints, 29 had three, and 9 had all four. Some were in service in the Army, but the larger number were wives of servicemen. Only eight of the group were over 34 years of age. At least fifty additional women were treated; but, because of difficulty in follow-up, they have been excluded from this study.

Method

After a careful history and physical examination, one 5 mg. tablet of diethylstilbestrol was given orally each day for twenty days. It was started at the end of a menstrual flow to avoid interrupting the cycle, and at bedtime to minimize nausea. The patient was instructed to report any unusual symptom and to return for re-examination at the end of the twenty-day period. At this time her symptoms were reviewed, and the pelvic examination was repeated. No other medication was given. Subsequent visits were governed by the patient's need for examination. A questionnaire was sent to those who had left the vicinity. These patients were followed sufficiently long to observe the results of therapy, more than seven months in the majority of cases. Ten per cent had endometrial biopsies at the start of the case, but because the patients changed their residence frequently, it was not possible to follow the ovarian function by repeat biopsies.

Results

Immediate Reaction to Diethylstilbestrol.—Approximately one-half of the patients had some nausea for the first two or three days. Nine and three-tenths per cent stopped taking the drug because of extreme nausea. If the patient persisted in taking the medication for three or four days despite the nausea, this symptom was not noted during the rest of the period of treatment. Very few patients had some nausea during the entire course. It was found that if 5 mg. of diethylstilbestrol produced extreme nausea, 0.1 to 1 mg. also produced extreme nausea with no chance of building a tolerance to the larger dose. The breasts became more sensitive and fuller in most instances, and a marked increase in secretion from the cervical glands occurred. Some patients noted thickening of the waist and puffiness of the ankles. The general symptomatology was that of early pregnancy, and suggests the possibility of a causal relationship between high estrin in early pregnancy and the symptoms which are considered to be physiologic at that time. Nervousness was often relieved during the treatment. Uterine bleeding during the course of therapy was unpredictable. A menstrual flow, due during this time, sometimes came as usual and sometimes was prevented from coming. It was normal, or abnormal in amount and duration. Because this aberration upset the patient's peace of mind, therapy soon was started at the end of a menstrual flow. Withdrawal bleeding occurred within eight days in all cases except two. One of these became pregnant during treatment and the other suffered from hypomenorrhea, secondary to "temporary" roentgen-ray castration which had been done some years previously for menorrhagia. This withdrawal bleeding varied from one day to two weeks and varied in amount and duration. Although it was almost always painless, its nature gave no clue to the subsequent menses. The next menstrual flow occurred twenty-eight to thirty-five days later and was designated as the first normal menses, i.e., the first bleeding to occur as the result of the cyclical activity of the ovary.

Dysmenorrhea.—Seventy patients complained of dysmenorrhea. This was classified severe if the pain necessitated bed rest, but if the pain required analgesics without bed rest, it was called moderate. Thirty-seven patients had either no pain or only an occasional cramp and were considered not to have dysmenorrhea. Table I shows the results in cases of dysmenorrhea, several months after the original course of therapy, when the patient was not taking any medication of any kind. Of the 55 who completed the course of treatment and were followed up successfully, 17, or 31 per cent, were completely relieved; 14, or 25 per cent, were changed from severe to moderate; and 24, or 44 per cent, were not helped. Three patients with severe dysmenorrhea were completely relieved for several months, but two of these had relapses due to environmental change and the third due to a heavy factory job. These were included in the moderate improvement column. A total improvement of 56 per cent, while not ideal, is encouraging in this difficult problem. Bleeding during the course and the withdrawal bleeding at the end of the course of therapy were almost always painless, as has been shown by many workers, with smaller doses of estrogens. It is subsequent menses that prove the success or failure of the treatment.

TABLE I. EFFECT OF DIETHYLSTILBESTROL ON DYSMENORRHEA

	NO IMPROVEMENT	MODERATE IMPROVEMENT	COMPLETE RELIEF	NOT KNOWN	INCOMPLETE TREATMENT	TOTAL
Severe dysmenorrhea	16	14	11	5	5	51
Moderate dysmenorrhea	8	0	6	3	2	19
TOTALS	24	14	17	8	7	70
Total improved 31						
Total unimproved 24						
No dysmenorrhea			34		3	37
						107

Cystic Ovaries.—Almost 50 per cent of patients in the series had enlargement of one or both ovaries. These varied in size from 3 to 15 cm. in diameter. The 3 cm. size was a round, tense, cystic ovary, not much larger than normal, but definitely abnormal in shape and texture. In thirty-three of fifty-one cases in which ovaries were enlarged, one or both ovaries exceeded 5 cm. in diameter. Pelvic pain, which was a prominent feature, caused 28 of the 51 patients to seek relief and necessitated hospitalization for three of these. Crossen[1] and other writers have stressed the need for conservatism in treating these cases. Many simple cysts disappear spontaneously, as any gynecologist knows. Table II shows the results after the course of diethylstilbestrol. Only 6 of 47 patients who completed the course of treatment still had adnexal enlargement, but only two proved to be cystic ovaries which had not responded to treatment. The other four included three inflammatory masses and one dermoid cyst, which was removed surgically. Four patients had recurrence of the cystic condition of the ovaries, but none of these was symptomatic. The ovaries were usually normal at the end of twenty days although some larger ones took six to twelve weeks to reach normal size. Reduction in size was apparent, after three weeks, even in these.

TABLE II. EFFECT OF DIETHYLSTILBESTROL ON CYSTIC OVARIES

Returned to normal	37
Not known	4
Incomplete treatment	4
No improvement	6
	51
No Improvement	
Dermoid—operated	1
Inflammatory disease—operated	1
Inflammatory disease—suspected	2
Cystic ovaries—operated	2

TABLE III. EFFECT OF DIETHYLSTILBESTROL ON MENSTRUAL DISORDERS

	NORMAL	IMPROVED	NO IMPROVEMENT	NOT KNOWN	INCOMPLETE TREATMENT	TOTALS
Less than 24-day cycle and/or profuse flow	13	7	7	6	2	35
More than 35-day cycle	5	7	6	0	1	19
Cycle 24 or less, to 35 or more days in same patient	4	1	1	0	0	6
Continuous bleeding up to 120 days	13 (stopped in 1 to 4 days)		1	0	0	14
Totals	35	15	15	6	3	74*

*Includes one patient counted in two columns.

Menstrual Disturbances.—By far, the commonest type of menstrual disturbance was excessive or too frequent flowing, including 49 of 74 cases. These were further divided into 14 cases of continuous bleeding and 35 cases of too frequent or too profuse periods. Although many patients with continuous flowing had bled for several weeks, they ceased flowing in one to four days with one exception. This result, with others of this group, is shown in Table III, and compares favorably with results obtained in constant bleeding by the Durham, North Carolina, group.[2, 5] One patient who was a failure in this hypermenorrhea group, and is over

40 years of age, is now in Colorado where she expects soon to have a radium-induced menopause. Another failure had an intramural, uterine fibroid, 3 cm. in diameter, and a solitary cystic ovary. The ovary returned to normal size, but a hysterectomy was necessary to control the excessive monthly flow. Only seven cases, including the two just mentioned, could be listed as unimproved. Half the patients with menorrhagia had cystic ovaries. Of the patients whose menstrual interval was more than thirty-five days, twelve became normal or improved, and six remained unimproved. One of six patients with markedly irregular cycles was not improved. Seventy per cent of all menstrual disturbances were completely relieved or greatly improved.

Infertility.—The question of fertility was added to this study when it was seen how often infertility occurred in relation to the other "functional" complaints. Because of the temporary tenure of these patients, the majority were not interested in a complete infertility investigation. Consequently, results shown in Table IV do not represent an exhaustive study. Since many patients were unmarried and some married women practiced contraception, the thirty-seven cases do not represent a true incidence of infertility in the group. All thirty-seven women had remained infertile at least ten months. Following the diethylstilbestrol course, several women who had been "infertile" less than ten months, became pregnant, but these could be considered coincidental and were excluded from tabulation. Only twenty-three patients reported who were living with their husbands and who had completed their course of treatment. Seventeen were not pregnant. Of these, one is to be operated upon for persistent adnexal masses, probably inflammatory. Two others have husbands whose sperm is totally inadequate. One of six who became pregnant had a husband whose sperm was inadequate, but improved after hormonal therapy. Two women are still pregnant; two had normal children; one had a stillborn child; and one had an abortion at three months after a long auto trip.

TABLE IV. EFFECT OF DIETHYLSTILBESTROL ON INFERTILITY

Not with husband, after treatment	4	
No pregnancy	17	74%
Pregnancy	6	26%
Not known	7	
Incomplete treatment	3	
Total	37	100%

Discussion

The most encouraging feature of this study is that favorable results persisted for several months after cessation of all medication. Whether this is a true ovarian stimulation cannot be said from this purely clinical work. Endometrial biopsies and hormonal assays before, and again a month after the conclusion of treatment might clarify this point.

It has long been known that there is a relationship between ovarian function and nervous activity. In the menopause, failing ovarian function seems to produce "nervousness." On the other hand, emotional shocks often induce amenorrhea or menorrhagia. Some patients in this series voluntarily reported a great improvement in their nervousness following treatment. Some other patients, who were very nervous, showed no improvement either in their nervousness or in their pelvic complaint. No conclusions can be drawn from this, but it again emphasizes the close relationship between the ovaries and the nervous system.

Improvement in patients with dysmenorrhea was maintained in 56 per cent without altering the cycle each month. This compares favorably with other methods of control, but is not to be considered the final solution of the difficulty. Estrogens have been shown by others to relieve dysmenorrhea, if given during the first half of the cycle each month. But an anovulatory cycle which is not desirable is produced. The single course of large doses of diethylstilbestrol probably produces only one anovulatory cycle and so overcomes that objection.

Cystic ovaries responded readily to the medication used. No doubt many would have become normal without treatment, but many patients had been ad-

vised elsewhere to have the pelvis explored surgically. Surgery for enlarged ovaries should not be advised without re-examination after a few weeks. This waiting period can be used for a course of diethylstilbestrol. If the ovary has not been reduced in size, surgery is indicated.

Many writers on hormonal subjects do not distinguish between the effect of small and large doses of diethylstilbestrol. It is well established that small doses cause thickening of the endometrium and, eventually, bleeding. I have confirmed the work of Karnaky[4] and of the Durham group[2, 5] by arresting prolonged uterine bleeding with large doses of this substance. It is less effective in regulating abnormal length of the menstrual cycle, but is more successful than many reported techniques.

No definite statement can be made as to the value of this medication in infertility except that it is worthy of further study.

The high percentage of success achieved in using a single type of treatment for multiple functional complaints suggests that they have a single cause, a malfunctioning ovary, and that the various disorders considered are different manifestations of the same underlying pathologic physiology.

Summary

1. Diethylstilbestrol was given orally in doses of 5 mg. daily for twenty days to 107 women with 232 functional ovarian complaints. Symptoms resulting from its use were described.

2. Partial or total relief was obtained in 56 per cent of patients with dysmenorrhea.

3. Ovaries returned to normal size in 37 of 47 patients with cystic ovaries.

4. In 13 of 14 patients, continuous uterine bleeding ceased after one to four days. Of all menstrual disturbances 70 per cent were partially or entirely corrected.

5. In an admittedly incomplete study on infertile women, 26 per cent conceived.

6. It was suggested that all the disorders considered are but different manifestations of a malfunctioning ovary. From a clinical standpoint, diethylstilbestrol, in the dosage used, corrected the manifestations of ovarian dysfunction in a majority of the cases.

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MESENTERIC THROMBOSIS COMPLICATED BY DERMOID CYST

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ALTHOUGH cases of mesenteric thrombosis are relatively few, they are important out of proportion to their number because of their severity and grave prognosis. An early diagnosis is often precluded because initial symptoms are not indicative of the condition and could be those of other intra-abdominal emergencies.

A few presenting symptoms, occurring in practically all recorded cases, suggest occlusion of a mesenteric vessel strongly enough to warrant a correct diagnosis. The following case report and a brief summary of the literature are offered to emphasize these symptoms in order to encourage a better prognosis. In addition the interesting complication of a dermoid cyst arising in the left ovary is described.

Persons of any age may be attacked by mesenteric thrombosis, but most cases occur about the time degenerative diseases begin. The average age is usually from 43 to 45 years, males predominating by about 40 per cent.

Mesenteric occlusion may be arterial, venous, or a combination of both. In arterial occlusion either embolism or thrombosis may precede, while in venous occlusion thrombosis has always occurred. The resulting infarction usually leads to necrosis of the adjacent intestinal wall, with resulting peritonitis and gangrene. The affected bowel then becomes dark red, with swollen mucosa and a lumen filled with hemorrhagic material.

The intestine involved may be anywhere from a few inches to the entire small bowel. Brown mentions the average length of affected intestine in 22 patients who recovered as 38.1 inches, and as 102.4 inches in 39 who died.

Causative lesions of venous and arterial occlusions of the mesenteric vessels are many. Among them are portal obstruction, cardiac conditions, septic abdominal lesions, intimal lesions, peripheral sepsis, degenerative diseases such as arterio-sclerosis, and mechanical damage arising from hernia, surgery, and obstruction. Ochsner includes long period alcohol consumption as causative. Green records fatigue and prolonged emotional strain as etiological factors. In many cases there is no apparent cause.

In its clinical features, mesenteric thrombosis is characterized primarily by pain, which may be dull and cramping or sudden and severe. It is usually centrally located, incessant, and not accompanied by muscular spasm or extreme tenderness before gangrene and peritonitis develop. Giamarino states that the pain tends to become colicky in about 50 per cent of the cases.

Localization of pain does not occur early and therefore rarely gives a definite clue for early diagnosis. When the pain is localized, it is more often in the lower right quadrant. In the following case and two previously reported in the literature, the onset of pain was in the lower left quadrant. Klemp believes that thrombosis of the inferior mesenteric vein gives rise to pain predominately on the left side, while thrombosis of the superior mesenteric vein produces pain mainly on the right side.

Three points upon which authorities agree as distinctive features of the pain of mesenteric occlusion are: (1) that it is more severe than the clinical findings warrant; (2) that it is not alleviated by morphine; and (3) that there is much less tenderness than would be looked for with such intense pain.

Various other symptoms may be found in mesenteric thrombosis. Vomiting is more common in arterial than in venous occlusion. Whittaker and Pemberton say that it occurred in about 75 per cent of the cases of arterial and combined arterial and venous occlusion, and in 50 per cent of the venous cases. Shock is another symptom that is not always present, but it is marked in fulminating cases and may appear in others in proportion to the mesenteric involvement. Constipation or diarrhea accompanied by bloody stools may be coincident, the former being more common.

Pallor and restlessness are often noted at the onset, but they are more marked later, being less evident in the early stages of venous than in arterial cases. Peristalsis is diminished, free fluid can usually be detected in the abdomen, and at times palpation demonstrates swollen intestinal coils. Rigidity and distention, if they do appear, are late symptoms. Distention is probably present in less than half the cases and is usually moderate, being more frequent in venous than in arterial thrombosis.

The leucocyte count and pulse rate furnish valuable clues to mesenteric occlusion because they are both almost uniformly high out of proportion to the temperature, which, like the blood pressure, is usually low. There may be a leucocytosis of 35,000 or more in arterial occlusion, while in venous occlusion there is a leucocytosis of approximately 20,000. The rapid pulse tends to become thready and slow, as the disease progresses.

The differential diagnosis includes ruptured peptic ulcer, various blood dyscrasias, and pelvic conditions such as ectopic pregnancy and torsion of pedicle of ovarian cysts.

The treatment of mesenteric occlusion is, of necessity, surgical. Exploratory laparotomy should be undertaken as soon as the condition is suspected, because the surgical risk greatly increases with the development of gangrene of the intestine. The affected portion of the gut, or the part nourished by the occluded vessel, must be resected and a fan-shaped portion of mesentery removed, following which anastomosis of the intestine and union of the mesenteric edges is accomplished. The postoperative treatment is supportive.

Case Report

The patient, Mrs. V. G., white, aged 39 years, was seized with severe pain in the lower left portion of the abdomen while eating her evening meal about 6 P.M. on May 31, 1944. A physician was summoned when nausea and vomiting occurred. The pulse was of good quality, and the patient did not seem shocked. No relief from pain being obtained from ¼ grain of morphine and $\frac{1}{150}$ grain of atropine and 3 grains of nembutal, she was sent to the hospital by ambulance. On admission to the Fayetteville City Hospital at 8:30 P.M., the patient was in excruciating pain localized in the lower left quadrant. She was moaning and had poor control of herself. The patient had had dysuria and pain in the left lumbar region on the preceding day. She had been married sixteen years. Her husband was living and well. She had two children, ages 15 and 4 years, both normal pregnancies and deliveries. There had been no serious illnesses, but for the past two years she had been extremely nervous and morose, and refused to live with her husband when he accepted a position in another city. Sixteen years previously, the right tube, ovary, and appendix were removed surgically. Menstrual periods had been regular with onset at 13 years of age and interval of twenty-eight days. The last menstrual period was May 16, 1944. The family history was irrelevant.

On physical examination, the face was colorless, lips blanched, and gums pale. The tongue was clear, the pharynx was not congested, and the tonsils had been removed. The

thyroid was palpably enlarged. No cervical adenopathy was present. The thorax was well developed. The heart was not enlarged, but the sounds were slow, weak, and of poor quality. No murmurs were present. Lung expansion was good, with the note resonant to percussion. Respirations were 25. There were no râles on cough. The abdomen was relaxed, with rounded contour. A midline scar from the symphysis to the umbilicus was present. No masses were palpable. Extreme tenderness was elicited over the lower abdomen above the bladder, particularly on the left side, and with deep pressure over the left lumbar area. Pelvic examination showed good perineal support, and no discharge or bleeding. The cervix was in midposition, not eroded, and the fundus small and anterior. There was fulness in the cul-de-sac and pain with upward pressure in this area. No masses were outlined in either fornix. The extremities showed no pathology.

Following admission to the hospital, the patient was given ½ grain of codeine with 2 grains of sodium luminal hypodermically. No relief followed. About 10 P.M. she became extremely shocked, cold and clammy, with pulse almost imperceptible. She rallied somewhat with external heat, but the pulse was extremely slow and weak. At this time the red blood count was 4,030,000, hemoglobin 100 per cent, leucocytes 15,050, with a differential of 88 segmented, 1 stab, and 11 lymphocytes. A catheterized specimen of urine was straw colored, reaction 7.5, specific gravity 1.020, faint trace of albumin, 1 plus acetone, with the microscopic examination negative.

The abdomen, which had been soft on admission, became rigid in the lower portion. In the lower left quadrant an indefinite mass extending about 5 fingerbreadths above the symphysis could be palpated. By vaginal examination a mass could now be palpated in the left fornix.

The patient became more restless and her condition was grave. Consultation was obtained and exploratory laporatomy was advised. A differential diagnosis was made of (1) left ovarian cyst with torsion of the pedicle and hemorrhage into the cyst, and (2) ruptured ectopic pregnancy in the left tube.

Laparotomy was performed about 1 A.M., June 1, 1944. Prior to surgery the patient was given 500 c.c. Beclysyl* intravenously. Nitrous oxide with oxygen was administered as the anesthetic over a period of one hour and twenty-two minutes. The blood pressure ranged from 90/40 to 100/60, the respiration rate was 20 to 30 per minute, and the pulse rate was about 70 per minute. Fifteen cubic centimeters of adrenal cortical hormone† and 500 c.c. Beclysyl were given to combat shock during the operation.

A midline incision was made from the symphysis to the umbilicus, to the left of an old scar. When the peritoneal cavity was opened, a small amount of serosanguineous fluid appeared and a gangrenous loop of ileum presented in the wound. About 48 inches of gut were clamped off and the affected portions excised, together with a V-shaped section of the mesentery. After the raw edges of the mesentery were united with continuous intestinal suture to control hemorrhage, a Murphy button was placed in the usual manner in each end of the intestine and the buttons united. Further approximation of the intestine was accomplished with a continuous suture uniting the serosa around the circumference of the button. Five grams of sulfanilamide powder were sprinkled in the wound, a flaccid drain inserted, and closure made in layers. The wound drained a large amount of serosanguineous fluid and the fatty tissue and skin bled freely, hemorrhage not being entirely controlled. The uterine fundus was anterior, the right tube and ovary had been removed, and the left tube and ovary were apparently grossly normal except for adhesions in that area.

The pathologic report showed a hemorrhagic infarction of the intestine.

The patient had a stormy postoperative course. Nasal suction was continued for about ten days, during which time the rectal temperature remained around 103° to 104° F., and the pulse was 120 to 140. Most of the time the patient was irrational. Treatment was supportive. On June 10, fecal matter began to drain from the wound and the abdomen was distended. Three transfusions of 500 c.c. of citrated blood were given by the indirect method on June 14, 15, and 16. Even as late as the twenty-fourth postoperative day the abdomen was still distended, the nasal tube was inserted at intervals, and the patient at times would become cold and clammy as if in shock. The superficial sutures for the most part sloughed out, and the deep sutures were removed on July 13, the forty-third postoperative day. On July 14 the patient sat up in a chair. On July 19 the Murphy button was removed manually

*Abbott Laboratories.
†Upjohn.

from the rectum. The patient was discharged July 23, the fifty-third postoperative day. At this time the wound was still draining some fecal material, but the patient was having normal stools.

The course was uneventful following her return home, the fecal fistula closing in about two weeks. From then on the patient was able to resume most of her usual housework and had no complaints. Upon coming into the office, Sept. 29, 1944, for routine follow-up, a pelvic examination disclosed a large mass in the pelvis. The abdominal wound was entirely healed, and there were absolutely no complaints indicative of the growth, although the patient stated that she had seemed to gain weight excessively for the past month. The menstrual periods and bowel movements were normal.

The mass steadily enlarged in size, but operation was not advised until later because of the patient's recent critical condition. Operation was undertaken, however, when difficulty in voiding became apparent. The patient was admitted to the hospital again on Nov. 17, 1944. The three days prior to surgery she had nausea, vomiting, and diarrhea, with temperature of 100° to 102° F. Physical examination on admission was essentially negative except for the pelvic condition. The vaginal examination showed good support. The examining finger met a mass that made the cul-de-sac protrude, practically filling the vagina. The cervix was pushed forward under the symphysis pubis and was extremely difficult to palpate, and impossible to expose to view with the speculum. The mass was densely adherent, tender, and seemed to have two portions, the one on the right side extending upward to a greater extent than the one on the left.

Operation was performed on Nov. 20, 1944. The incision had to be made far to the right of the midline to avoid the old scars. Upon entering the peritoneal cavity, a large dermoid cyst was found supplanting the left ovary, adherent to the uterus, tube, omentum, and intestines. The uterus was drawn over to the right side, and the mass, which at first was impossible to outline, seemed to push the uterus and bladder forward and occupy the entire pelvis. The cyst extended deep into the vagina, particularly on the right side, and was adherent throughout. In breaking up the adhesions, the cyst wall was ruptured and a large amount of gray, cheesy-looking material and many long hairs were liberated. The tube and pedicle of the cyst were twisted twice at the base, and this area was clamped. In freeing the remainder of the cyst, a large abscess cavity posterior and to the right was entered and drained. The stump of the broad ligament and tube was ligated. Five grams of sulfanilamide powder were dusted into the area. A flaccid drain was put deep in the right side of the pelvis and the abdomen was closed in layers.

The patient reacted well from the anesthesia, and the postoperative progress was uneventful except for delayed healing of the lower portion of the wound. The drain was removed at the end of forty-eight hours, the superficial sutures on the tenth day, and the deep sutures on the twelfth day. The patient left the hospital on the fourteenth postoperative day, with the lower portion of the wound unhealed, but otherwise in excellent condition. At the present time, three months after the operation, the patient seems to be entirely well.

Discussion

This case of mesenteric thrombosis, later complicated by a dermoid cyst of the left ovary, is offered with a brief recapitulation of the literature to emphasize the presenting symptoms common to the majority of such cases, and to state the belief that if the treatment is always surgical with no preface of conservatism and delay, the mortality will be lowered.

In the presence of a pain that indicates an intra-abdominal catastrophe localized to either lower quadrant, one should remember that mesenteric occlusion can be localized in either quadrant when the affected portion of the bowel forms a mass, and can be readily confused with pelvic conditions, such as ovarian cyst and ectopic pregnancy.

Upon considering the possible sources for the mesenteric thrombosis in our case, the most likely causes seem to be the fact that the patient had entered the age of degenerative disease and that she had been under emotional strain for two years.

The occurrence of the cyst was probably unrelated to the mesenteric thrombosis, but it is interesting to speculate whether elements contributing to the

growth of the cyst were present in sufficient amount at the time of the first operation to have been the causative factor in the forming of the embolus.

Summary

1. The etiology and clinical picture of mesenteric thrombosis is offered from our case report and from a brief review of the literature.

2. Etiologically, mesenteric occlusion can result from mechanical damage, peripheral sepsis, portal obstruction, inflammatory abdominal lesions, degenerative diseases, cardiac diseases, and less definite causes such as excessive alcohol consumption and emotional strain.

3. The commonest early symptom is intense pain, not relieved by morphine, and out of proportion to the mild clinical findings.

4. Other symptoms may include pallor, restlessness, vomiting, constipation or diarrhea, tenderness, rigidity, shock, leucocytosis, and rapid pulse rate, low temperature and blood pressure, with a possible rise in temperature as a very late symptom.

5. When the pain becomes localized in either of the lower abdominal quadrants it can readily be mistaken for a gynecologic condition.

6. In our case, there was no causative lesion determined. The most likely factors seem to be the patient's age and the emotional state. The early appearance of the cyst after the first operation suggests a mere possibility that it may have been the cause of the embolus.

7. The present high mortality of this disease can be reduced by immediate surgery upon suspicion of the condition.

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A SEVEN-YEAR REVIEW OF ECLAMPSIA WITH SPECIAL REFERENCE TO TREATMENT WITH VERATRUM VIRIDE

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DURING the past fifty years innumerable methods of treatment for eclampsia have been advanced. Some of these have held their place in the armamentarium but many have fallen by the wayside. It is one from the latter group that, it seems, should still have a definite place in the therapeutic role, namely, *Veratrum viride.*

It is true that this was not discarded by all and that many general practitioners in the South and even some of the Medical Centers continued to use this routinely. I refer particularly to the Department of Obstetrics at the University of Cincinnati. In the October, 1940, issue of the *Journal of the American Medical Association,* Dr. Flemming and Dr. Bryant, of the Department of Obstetrics at the University of Cincinnati School of Medicine, reported a study of 120 cases on which *Veratrum viride* had been used with only 1.6 mortality, and even those included in the mortality group, on further investigation, could hardly be included in the group of failures. It was from this report that further interest was aroused for this particular method of treatment.

Soon after joining the resident staff of Obstetrics at the John Gaston Hospital, Memphis, Tennessee, in July, 1941, permission was obtained from Dr. W. T. Pride, Chief of the Department of Obstetrics and Gynecology at the University of Tennessee School of Medicine, to begin the use of this drug in the treatment of eclampsia where a number of such patients are encountered each year. We used very much the same method as that outlined by Dr. Flemming and Dr. Bryant except for minor modifications at times which will be mentioned later in this report.

After using *Veratrum viride* for approximately one year with uniformly good results, it was suggested by Dr. J. R. Rheinberger, Associate Professor of Obstetrics, that we make a seven-year study of treatment of eclampsia as followed in our hospital, using for a comparative study the last year, during which time *Veratrum viride* had been used. This was done and our report deals with the years 1936 to 1942 inclusive. During these seven years 150 cases were diagnosed as eclampsia of pregnancy.

Methods and Treatment

We group our toxemias in Grades I, II, III, and IV. The Grade I were those with only mild symptoms of toxemia; Grade II, those of the pre-eclamptic group; Grade III, those of the definite eclamptic group; and Grade IV, those who may have convulsions and appear at first to be true eclampsia, but on further investigation reveal definite kidney damage which may have been present prior to the pregnancy. It is my opinion that our method of treatment has no definite place and is of little value in Grades I, II, and IV, only being of value in Grade III, true eclampsia.

We do not hesitate to use the drug in questionable cases of eclampsia where the diagnosis is not certain. We have our patients constantly attended, usually by senior medical students, until the patient is rational.

*Family physician for the Quantico Marine Base.

Instructions for Treatment of Pre-eclampsia and Eclampsia

1. Give 5 to 10 minims (0.3 to 0.6 c.c.) of *Veratrum viride* immediately; repeat every fifteen minutes unless the pulse rate is below 60 or the blood pressure is below 120 systolic; thereafter, until the patient is conscious, repeat in 3 to 10 minim (0.2 to 0.6 c.c.) doses if the pulse rate goes over 80 or the blood pressure over 150 systolic; after the patient is conscious and cooperative, give 3 to 10 minim doses if the patient is nauseated or has severe headache, marked visual disturbances, or epigastric pain or convulsions.

2. Give 6 c.c. of 50 per cent magnesium sulfate by deep injection immediately, 4 c.c. every six hours for four doses, and then 4 c.c. every twelve hours for four doses.*

3. Give 500 c.c. of 20 per cent dextrose intravenously at once; repeat every eight hours until consciousness returns.

4. Catheterize and give a soapsuds enema immediately.

5. Check the pulse and blood pressure hourly as long as coma persists, then every two to four hours while the patient is awake.

6. Force fluids (3,500 c.c. daily) by mouth as soon as possible.

7. Give no sedatives except for extreme restlessness or labor.

8. Institute a diet free of salt as soon as tolerated.

9. Measure the fluid intake and the urinary output; examine the urine daily for albumin.

TABLE I. TABULATION OF CASES
1936 to 1942

Negro patients	129
White patients	21
Total	150
1936 to 1941	
Maternal mortality	35 or 26%
Infant mortality	42 or 50%
1942	
Maternal mortality	0
Infant mortality	2 (?) or 6%

Pharmacology of Veratrum Viride

Veratrum viride is an alkaloid, and is derived from the roots and rhizomes of hellebore. This plant is indigenous to both Europe and North America. The drug acts as a cardio-inhibitor, vasodilator, and antipyretic. It is toxic in large doses and must be given carefully. Toxic reactions include sudden drop in blood pressure and pulse rate, nausea and vomiting, and eventually coma. Toxic reactions may be counteracted by gastric lavage or atropine in the usual dose. The preparation used was Veratrone† in doses of 3 to 10 minims, given by hypodermic injection.

Comment

Since there are many more Negroes in the South, it was with these that most of our study was made. Out of the 150 cases, 129 were Negro and 21 white, a ratio of nearly 6 to 1. Many of these never attended a prenatal clinic as is well shown here in that 71 of 150 cases were nonclinic patients. Table I shows the comparative percentage mortality in the mothers and infants for the seven-year study. It is to the year 1942 that we wish to pay special attention. However, our cases are only 15 in number and of these, 14 received *Veratrum viride*. With this reduction in number of actual eclampsias, there were still almost 50 per cent that were nonclinic patients. This brings out the important role of prenatal care. It was noted that over 50 per cent of the cases were in women 20 years of age or younger. It occurs to me that this disease, true eclampsia, is far more frequent in women of this age group and is due to the

*In a number of these cases the 50 per cent magnesium sulfate was omitted from our treatment regime, and only the concentrated glucose was used. There did not seem to be any marked difference in response in these cases.

†Parke, Davis & Company.

lack of care. This is especially true in young Negro girls to whom the responsibility of childbearing is of minor significance and is given little consideration.

Of the 150 cases in this review, 104 were primigravidas, revealing that true eclampsia is far more frequent in this group. If those patients diagnosed as eclampsia who have had several children and are in the later years of childbearing are studied carefully, it will be found that a large number of them fall into Grade IV where chronic kidney damage has been present for some time. In this group we do not believe *Veratrum viride* is of much value. In over half of the patients, the onset of eclampsia was in the antepartum period.

During these seven years, every method of treatment known seemed to have been given a chance at one time or another. Many sedatives were used, including morphine, magnesium sulfate, sodium bromide, chloral hydrate, and various barbiturates both orally and intravenously. In the earlier years of this study many supportive measures were given. Gastric lavage was used extensively. Concentrated glucose and even 20 per cent sucrose were used intravenously. On investigation, one of the fatalities was thought most likely due to the latter. Digitalis was given in many cases seemingly as a prophylactic measure. This drug was used in five of the seven years reviewed and is still being used for the same reason in some university hospitals. Salyrgan was used alone and in conjunction with digitalis. In reviewing many of these cases, there was no particular value that could be attributed to its use. This helped to further confirm the idea, already in mind, that digitalis has no place prophylactically or therapeutically in the treatment of eclampsia unless decompensation or auricular fibrillation is present.

In the year 1937 many cesarean sections were done. It was in this year that the mortality reached its highest peak. Nine sections were done out of 20 cases (45 per cent) for that year. Seven of the nine patients expired. Five of the seven cases were treated in the hospital for only twenty-four hours or less before operation was performed. All of these expired. This emphasizes the urgent need for control of the eclampsia before any operative measure is attempted.

We had fifteen cases for 1941 to 1942. Fourteen of these cases received *Veratrum viride*. All of them recovered. We attempted to treat our patients without giving any morphine or barbiturates. We do not feel that a definite sedative is indicated unless the patient is in labor. In some instances they were given through error. Here we feel that paraldehyde per rectum is the drug of choice. It was found that after treatment had been started, 50 per cent or more of our patients did not continue to have any convulsions, at most only two convulsions, and that in a short period of time the patient would be rational and responding to questions.

We feel that no attempt at delivery should be done until the convulsions have been controlled and the patient is rational for one or two days. We have found that a number of these cases will go into labor spontaneously during this period and, if not, that induction of labor can be brought about by the simpler methods, such as medical inductions or some minor operative method such as rupturing of the membranes. A very small number may not respond to any of these. If the patient is a primipara near term, with a closed, thick cervix, a cesarean section can be considered and performed rather safely, provided the eclamptic state has been controlled for a time, but the patient is beginning to show evidence of returning to her former condition by blood pressure rise, increase in albumin and casts in the urine. We do not like to use bag inductions in the primiparas for this or any other reason.

If the patient shows symptoms of severe reactions to the drug such as were mentioned above, we think it best to discontinue this treatment and resort to some other measure.

Since the report on the cases of 1942, we have used this method of treatment and are continuing its use. We had one patient in 1943 who did not respond to our routine, and expired. Altogether, the treatment has continued to prove very successful. We have varied the routine and have tried leaving out the 50 per cent magnesium sulfate intramuscularly, and it would appear from the small number of cases so treated that results were probably as good. This was done at the suggestion of Dr. J. R. Rheinberger.

Conclusions

1. *Veratrum viride* has a very definite place in the treatment of eclampsia.
2. Its greatest usefulness is in true eclampsia.
3. If toxic reactions are shown, discard its use completely for that particular case.
4. No operative procedures should be instituted until convulsions are controlled and the patient is rational.
5. Digitalis has no place as a prophylactic drug for the heart, and its indications are those recognized by the cardiologist.
6. Eclampsia is a complication of pregnancy prevalent mostly among the young Negro woman in the South as the result of improper prenatal care.

I wish to acknowledge the assistance given by Dr. Everette Gustafson in compiling the material and preparing this report for publication.

CONTINUOUS CAUDAL ANALGESIA IN CURETTAGE FOR ABORTION

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THE prevention of blood loss during evacuation of the uterus by dilatation and curettage in therapeutic abortion and in incomplete abortion has long been recognized as an important factor in the control of morbidity and mortality. In hope of decreasing blood loss in these cases, we have in the past eight months employed continuous caudal analgesia in all instances except in the presence of recognized contraindications to caudal technique.

Choice of this technique stems from the observation that blood loss in the third stage of labor managed under continuous caudal analgesia generally is markedly reduced. The decrease in blood loss is attributed to increased contractility of the uterus. In contrast to the effect produced by general anesthetic agents, the motor elements of the active contractile portion of the uterus are not inhibited under the caudal technique if the analgesic effect is kept below the sixth thoracic segment. Cervical tissues, on the other hand, are relaxed through inhibition of their motor innervation.

Appreciating the uterine relaxing effect of general anesthetic agents, Taussig[1] recommended the use of local infiltration of the broad ligaments in cases of this type. Petersen[2] reported the utilization of spinal anesthesia in therapeutic abortion.

Technique

The technique used by us is based upon the method originally described by Hingson and Edwards.[3] Preoperative medication in the form of 0.2 Gm. pentobarbital sodium (Nembutal) is administered orally approximately thirty minutes before the patient is taken to the anesthetic room. With the patient on her abdomen, the lower back is surgically prepared and draped. Afer local infiltration of the skin, a malleable steel needle is inserted into the sacral canal through the sacral hiatus. When it has been determined that the needle is properly placed, a test dose of 8 c.c. of 1.5 per cent metycaine in Ringer's solution is injected. After a ten-minute period of observation, and in the absence of signs of spinal anesthesia, an additional 22 c.c. of the analgesic agent are injected, and the patient is placed immediately upon her back. Care must be taken to prevent displacement of the needle. The operating table is tilted into 5 degrees Trendelenburg position, the patient's feet are held upward for two or three minutes, following which the legs are suspended by stirrups in lithotomy position. After an interval of about ten minutes the level of analgesia on the abdominal skin is tested by means of a sharp needle. Blood pressure is checked at five-minute intervals during the entire procedure.

The need of subsequent injections of the analgesic agent is determined by the rapidity with which the analgesia progresses upward on the abdominal skin and the height at which it is stabilized. It has been our experience that an additional 10 to 20 c.c. injection is necessary in fifteen to twenty minutes. This usually carries the level of analgesia to the eighth or ninth thoracic segment. Some patients will experience pain when the curette is passed along the top of the fundus unless analgesia is established as high as the ninth thoracic segment.

During the operation an anesthetist is in constant attendance at the head of the operating table, checking the patient's blood pressure and noting her reactions. On completion of the operation, the needle is removed and the hiatal area is cleansed with an alcohol sponge. The patient is returned to her room and subsequently watched for delayed bleeding and fall in blood pressure, neither of which has occurred in our series. It is advisable to administer ⅙ grain morphine sulfate hypodermically before the analgesic effect wears off, to obviate the discomfort of postcurettage uterine cramps.

As will be noted in the accompanying chart, the amount of 1.5 per cent metycaine used has been relatively constant, the smallest total amount injected being 40 c.c. and the largest 70 c.c. The average dose has been less than 55 c.c. This variance in amount necessary to produce satisfactory analgesia is probably due to individual susceptibility to the drug and to the size of the patient. The amount must be regulated by objective and subjective findings.

At first we used vasopressor agents prophylactically to prevent fall in blood pressure resulting from vasodilatation secondary to lumbar sympathetic block. Four patients received 50 mg. of ephedrine sulfate injected into the sacral canal with the preliminary 8 c.c. dose of metycaine, and in one other case 25 mg. of the same drug were used. Intramuscular injection of 2½ mg. of neosynephrin hydrochloride early in the induction was used in two cases and 50 mg. of ephedrine sulfate were used similarly in another case. In the latter part of our series we found that it was not necessary to use a vasoconstricting agent routinely if the operating table was put into 5 degrees Trendelenburg position and the legs of the patient elevated as soon as she was placed upon her back.

The only other supplemental medication used in this series was ergotrate 0.2 mg. given intravenously in six cases in which the uterus felt boggy. In none of these was bleeding excessive. In all but three cases an intravenous infusion of 5 per cent glucose was started preoperatively. This procedure has been routine in cases done under general anesthesia, where blood loss is anticipated.

Clinical Material

In this preliminary report we are presenting 22 consecutive cases curetted under the caudal technique described above. The first case was a therapeutic abortion performed at ten weeks of pregnancy for far-advanced pulmonary tuberculosis. The remaining 21 were incomplete abortions wherein curettage was deemed advisable.

Eleven of the patients were nulliparas and an equal number multiparas. Ages ranged from 18 to 37 years, with the average at 26.6 years.

Duration of the pregnancies ranged from eight to seventeen weeks. The average gestation period in the series was twelve weeks. In the incomplete abortion cases there had been bleeding from three days to six weeks prior to curettage. The average duration of this symptom was thirteen days.

No case of incomplete abortion had to be curetted in the presence of signs of obvious infection in the pelvis. Diagnosis of incomplete abortion was confirmed histologically in all patients by the presence of decidual and chorionic tissue in the scrapings.

TABLE I. SUMMARY OF DILATATION AND EVACUATION UNDER CAUDAL ANALGESIA

PATIENT	AGE (YEARS)	PARITY	GRAVIDITY	DURATION OF PREGNANCY (WEEKS)	DURATION OF BLEEDING PREOPERATIVELY	AMOUNT OF 1½% METYCAINE C.C.	SUPPLEMENTAL MEDICATION	BLOOD LOSS (C.C.)
V. G. 544324	37	0	i	10	*	60	None	60
E. H. 510173	24	i	ii	13	11 days	60	Ergotrate 0.2 mg. I.V. Ephedrine 50 mg. into sacral canal	50
M. E. 459794	24	0	ii	12	8 days	60	None	10
E. H. 546063	22	0	i	13	7 days	40	None	40
E. B. 545052	27	v	viii	11	4 weeks	40	Neosynephrin 2.5 mg. I.M.	35
B. G. 521273	23	0	i	8	9 days	55	None	75
M. A. 544918	33	i	ii	17	12 days	45	None	10
A. S. 544878	23	0	i	11	17 days	40	Neosynephrin 2.5 mg. I.M.	50
N. W. 548085	24	i	ii	14	21 days	65	Ergotrate 0.2 mg. I.V.	125
M. S. 550035	22	0	i	11	3 days	40	Ephedrine 50 mg. into sacral canal	30
K. J. 479932	20	ii	iv	16	6 days	55	Ephedrine 25 mg. into sacral canal	25
R. M. 550912	28	iii	v	11	6 weeks	55	Ephedrine 50 mg. into sacral canal	10
R. H. 551345	26	0	i	11	14 days	55	Ephedrine 50 mg. into sacral canal	5
V. M. 517278	23	0	i	12	19 days	40	Ergotrate 0.2 mg. I.V.	30
M. P. 556600	27	iv	v	14	6 days	60	Ergotrate 0.2 mg. I.V.	25
A. H. 429803	29	0	ii	9	20 days	55	None	5
M. S. 189736	36	ii	iii	12	4 days	60	None	5
G. A. 559924	36	vi	vii	15	5 days	55	None	80
M. E. 459794	25	0	iii	9	19 days	70	None	35
S. W. 560594	26	i	ii	13	10 days	60	Ergotrate 0.2 mg. I.V.	35
D. H. 499652	34	iv	vi	12	10 days	40	None	55
R. S. 561008	18	0	i	12	7 days	70	Ergotrate 0.2 mg. I.V. Ephedrine 50 mg. I.M.	40

*Therapeutic abortion for far-advanced pulmonary tuberculosis.

Results

Blood loss in our 22 cases ranged from less than 5 c.c. to 125 c.c. Seventeen of the patients lost 50 c.c. of blood or less, and the average loss per patient was less than 40 c.c.

These figures compare with an average blood loss of 415 c.c. in twelve unselected cases of abortion curetted in this clinic under general anesthesia. In this group blood loss ranged from 75 c.c. to 1,100 c.c.

In the cases of our series as well as in the control group the blood lost from the uterus during the operation was collected in a pan placed beneath a grooved weighted retractor inserted along the posterior vaginal wall. To this amount was added all blood squeezed from gauze sponges used during the operation (not more than one or two sponges were used in any of the caudal cases), and the total was measured. Clots removed from the uterus were separated from the products of conception and added to the amount measured. An estimated additional amount was added to the measured volume in each case in lieu of the blood that might have been lost on sponges, instruments, or in the process of collection.

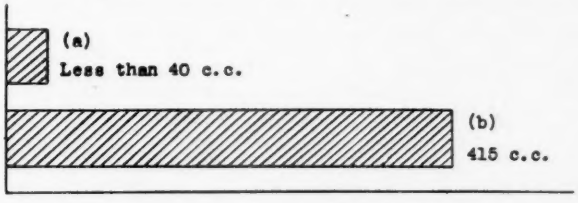

Fig. 1.—Comparison of average blood loss in curettage for abortion under (a) continuous caudal analgesia, (b) general anesthesia.

The blood pressure changes in this series of cases were not of appreciable significance. In only eight cases was there a systolic pressure fall of 20 mm. Hg. This blood pressure drop was transient, and no untoward symptoms were observed. In the remaining fourteen cases the blood pressure showed no significant deviation from the preinduction readings.

The postoperative course in all of the patients in this series was smooth and uneventful. The patients exhibited no febrile reaction, no blood pressure fall, no vomiting or abdominal distention, no urinary retention, no phlebitis, and postoperative discharge in no case was profuse. All patients were able to eat and drink immediately following the operation. The postoperative convalescence and return to normal activity is hastened, due in part to the absence of general anesthesia and certainly to the lack of significant blood loss at the time of curettage.

Summary

1. In an attempt to decrease blood loss at the time of therapeutic abortion and curettage for incomplete abortion we have used continuous caudal analgesia as an anesthetic method.

2. This technique maintains tonicity of the uterine muscle and at the same time provides analgesia of the perineum, vagina, and in the cervical and fundal portions of the uterus.

3. In 22 consecutive cases average blood loss was less than 40 c.c. per patient, varying from less than 5 c.c. to 125 c.c. Seventeen of the patients lost 50 c.c. or less.

4. There were no anesthetic, operative or postoperative complications.

5. Postoperative convalescence and return to normal activity of the patient is hastened.

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CLINICAL EXPERIENCE WITH A NEW SYNTHETIC ERGONOVINE-LIKE SUBSTANCE

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THE problem of the influence of oxytocic substances upon postpartum bleeding has long been a topic for discussion. Many have believed these drugs of little or no value due to several factors, among which have been the obvious uselessness of the drug in lacerations and the undependability of many of the various earlier preparations of ergot. Since the advent of ergonovine, however, greater numbers of obstetricians feel more confident that this drug has been of benefit, especially when given by the intravenous route.

By far the greater part of the ergot used in the United States is obtained from foreign sources, notably Russia and Spain, and it is entirely possible that, under certain conditions, such as war, drought, or blight, the natural ergot would not be obtainable in the necessary quantities. As a consequence, the development of a synthesized ergonovine-like substance would be an obvious advantage, for this reason as well as from the standpoint of permitting more accurate standardization.

It might be well to review briefly some salient points in the history of the development of the ergot alkaloids: In 1875, Tanret[1] obtained a crystalline ergotinine from ergot, but this alkaloid was only slightly active and possessed little or no pharmacologic or therapeutic significance. In 1906, Barger and Carr,[2] almost simultaneously with Kraft,[3] discovered ergotoxine in amorphous form. Ergotoxine has been recently crystallized and is isomeric with ergotinine, according to Stoll.[4] In 1920, Stoll isolated two new isomeric alkaloids, ergotamine and ergotaminine, from ergot, and in 1925 Stoeckel[5] at the Gynecological Congress in Vienna called attention to the regular and constant effect of ergotamine as a uterine styptic.

In 1935, four different investigators reported a new aqueous ergot alkaloid, since assigned the name ergonovine by the Council on Pharmacy and Chemistry. Dudley and Moir[6] called this ergometrine; Kharasch and Legault,[7] ergotocin; Thompson,[8] ergostetrine; and Stoll and Burckhardt,[9] ergobasine. Recently, Stoll and Hofmann[10] have synthesized, among other derivatives, d-lysergic acid d l hydroxybutyl-amide 2 also known as methylergobasine tartrate or Methergine.*

Chemistry and Pharmacology

The general formula of Methergine may be compared with that of ergonovine:

R† represents lysergic acid molecule.

Methergine has been found comparable in utero-activity to ergonovine on isolated uterine strips of both rabbit and guinea pig. It does not reverse the adrenalin response on isolated rabbit uteri as does ergotamine. The re-

*Methergine was supplied by the Sandoz Chemical Works, Inc.

laxing action on the isolated guinea pig jejunum indicates slight adrenergic effect. It has shown no effect on the isolated virgin dog and rat uteri.[11]

Clinically, in 200 cases of human administration, we have observed no toxic effects.

Physiology of Placental Separation

New theories have been advanced concerning the mechanism of the third stage of labor which provide a basis for the more modern application of oxytocic drugs in this stage.

Frankl originally believed that when the child was born, blood rushed into the placental site (a "*hyperemia ex vacuo*" mechanism), there was rhexis and blood extravasation in the decidua spongiosa, and a retroplacental hematoma was formed. With uterine contractions, this hematoma was driven as a fluid wedge between the layers of the decidua serotina, and the placenta was separated off.[12]

In the monkey, Danforth, Graham, and Ivy[13] observed almost complete separation of the placenta at the end of the second stage. Similar claim is made for the human by Leff[14] who states that the placenta separates immediately as the baby leaves the uterus. Usually, with the first uterine contraction there is marked diminution in the size of the placental site. The placenta shrinks somewhat, but not enough to compare to the placental site, and separation is inevitable.

Brandt[15] has proposed that "as the child is being expelled, in a normal labor, the size of the uterus diminishes partly as a result of muscular tone and partly due to uterine muscle contraction. As a result of this change, the veins in the muscle layer of the uterus are compressed so that maternal blood in the placenta cannot escape from the uterus. At the same time, the reduction in size of the uterine cavity has squeezed the placenta so that the blood in the intervillous spaces is forced into the veins of the decidua. We therefore have a layer of overdistended veins in the decidua spongiosa, lying between a firmly contracted uterine wall and a more or less solidly compressed placenta. As a result of this viselike compression, the congested venous sinuses burst and the extravasated blood under tension causes tearing of the very fine septa of the spongiosa, thereby detaching the placenta from its uterine site.

"For this normal mechanism to occur . . . contracted uterine wall and compressed compact placenta must be present. If either of these is absent, separation does not follow a normal course. If the uterus does not contract as the child is being born, then separation does not occur until an afterpain has set in, causing reduction in the size of the uterine cavity as well as contraction of the muscular wall of the uterus. On the other hand, if the placenta is thinned out and covers an area much larger than normal, there does not develop the usual counterresisting mass of compressed compact placenta; hence separation is delayed.

"As the separated placenta is detached from its uterine site, it folds on itself, but is held in the uterine cavity because of the firm attachment of the membranes. If the uterine contraction . . . is strong . . . the placenta may be expelled into the lower uterine segment and upper vagina. . . . When this occurs, the retroplacental hematoma does not form and could have no function."

Third Stage Technique

It is the purpose of oxytocic drugs given before the placenta is separated to induce the strong contraction of the uterus which results in the mechanism of the third stage described above. The preparation which we have used in our experiment has been used in very few cases by other observers[16, 17] who have "estimated" and not measured the blood loss in each case. We wish to present a preliminary report of our experience with Methergine in 200 cases.

In 1937 one of us[18] suggested that the administration of Basergin given immediately at the end of the second stage definitely shortened the third stage of labor and decidedly decreased postpartum bleeding. Subsequently, Davin,[19] in a larger series, made a similar recommendation with similar results.

In 100 cases, 1 c.c. of Methergine, containing 0.2 mg. per cubic centimeter, was given intramuscularly immediately following delivery of the placenta. In the other 100 cases, the same preparation and dose was given intravenously immediately following birth of the child and before the placenta was delivered. In both groups, the blood was measured as pre-

placental, placental, and for thirty minutes after birth of the placenta. No deductions have been made for bleeding from lacerations or episiotomies in the routine case.

In the cases handled by the intramuscular method, a modified Credé maneuver was used to deliver the placenta. In the cases handled by the intravenous method, the placenta was delivered in the following manner: The umbilical cord was clamped close to the vulva. The uterus was palpated to insure a firm contraction. The clamp at the vulva was then held firmly in one hand while the fingertips of the other hand were inserted abdominally between the fundus and the symphysis pubis. Upon elevation of the fundus toward the sternum, failure of the cord to retract into the vagina was taken as evidence of separation of the placenta and continued elevation of the fundus associated with minimal traction on the cord resulted in delivery of the placenta. Where the cord retracted into the vagina, the placenta was assumed to be attached or incarcerated, and no attempt was made to deliver the placenta until later repetition of the maneuver revealed its freedom.[15]

In all cases, the blood loss was measured accurately in the following manner: A sterile metal pan was placed beneath the patients' buttocks. Extending from this pan was a trough emptying into a graduated container which was at all times under the direct vision of the accoucheur. This container was on a movable arm which could be maneuvered by the operator's knee in order to avoid inclusion of amniotic fluid and other possible diluents. (Figs. 1 and 2.)

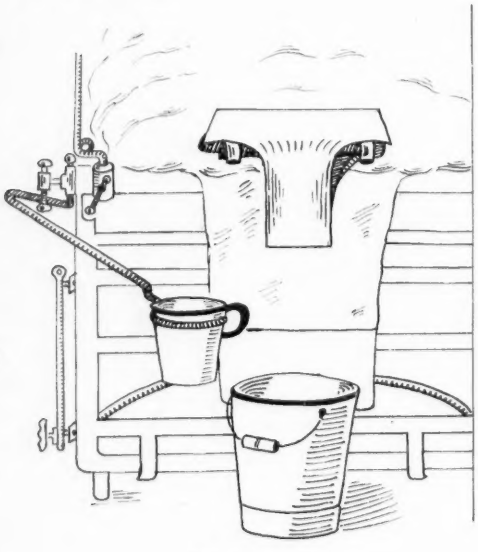

Fig. 1.

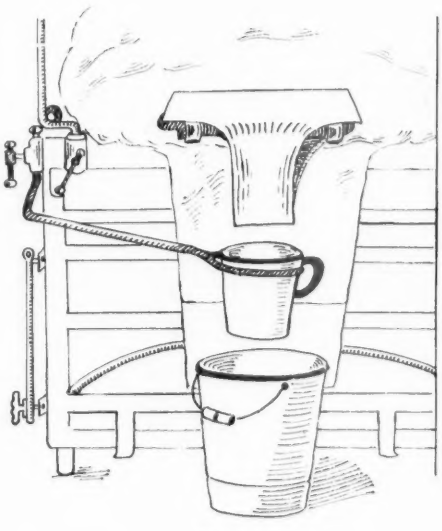

Fig. 2.

Analysis of Results

In both the intravenous and intramuscular groups there were 30 primigravidas and 70 multigravidas.

In the intravenous group, operative obstetrics was performed in 15 primigravidas and 5 multigravidas for an incidence of 20 per cent. In the intramuscular group, 9 primigravidas and 3 multigravidas, an incidence of 12 per cent, required intervention.

The average blood loss with the intravenous technique was a gross of 113.24 c.c. and a net of 90.35 c.c. The average blood loss for the intramuscular group was 168.07 c.c. gross and 159.68 c.c. net. In the intravenous group, the primigravidas averaged 116.03 c.c. gross, and 94.13 c.c. net, while the multigravidas averaged 112.05 c.c. gross and 87.22 c.c. net. In the intramuscular group, the primigravidas averaged 173.0 c.c. gross and net, while the multigravidas averaged 165.96 c.c. gross and 153.86 c.c. net. These corrections will be explained below.

The largest blood loss occurred in one case (No. 5) of the group receiving Methergine intramuscularly. However, in this instance, other factors which could not be controlled by Methergine or any oxytocic were felt to be responsible and will be dealt with in greater detail. The smallest blood loss occurred in the group receiving Methergine intravenously; in many of these cases the blood loss was so slight that it could not be measured.

The third stage averaged 7.68 minutes in the intravenous group and 10.38 minutes in the intramuscular group. No attempt was made to deliver the placenta as soon as it was separated. In most cases, the baby was attended and then the third stage was terminated. In spite of this, the third stage in both groups of cases was of shorter duration than the average time quoted as normal in textbooks.

Manual removal of the placenta was required three times in the intravenous group and not at all in the intramuscular group. In one of these three cases, the procedure was elective after 74 minutes in a nonbleeding third stage. The placenta here was found completely attached. The other two cases are included in the five cases for which we have offered correction in our results. These may now be explained:

CASE 1.—A. O. Delivered by low forceps and episiotomy of a 9-pound 8½-ounce male child. Methergine, 1 c.c., given intravenously. As soon as the baby was born, the episiotomy bled 600 c.c. from a large severed vessel despite immediate repair. Third stage completed with no additional blood loss.

CASE 2.—M. R. Delivered spontaneously of an 8-pound 9½-ounce baby. Given Methergine 1 c.c. intravenously. After 1½ hours with no sign of bleeding or separation, a completely attached placenta was manually removed. Due to deep anesthesia and resultant atonicity of the uterus, patient bled 1,000 c.c. and had to be packed. Past history revealed manual removal of the placenta with postpartum hemorrhage in her previous two deliveries.

CASE 3.—C. G. A 5-pound 13-ounce female child delivered from right occipitoposterior by manual rotation and extraction with DeLee forceps. Methergine, 1 c.c., given intravenously. After one hour with no sign of bleeding or separation, a completely attached placenta was manually removed with 500 c.c. blood loss.

CASE 4.—J. M. Delivered a 6-pound 9-ounce male child spontaneously. Given Methergine, 1 c.c., intravenously. Third stage terminated immediately. Due to moderate bleeding, inspection was made. A cervical laceration and clitoroidal laceration were both repaired. Blood loss totaled 500 c.c., practically all of which came from the lacerations.

CASE 5.—C. M. Spontaneously delivered an 8-pound 12-ounce child. Placenta delivered in six minutes without administration of oxytocic drugs. Sudden hemorrhage of 1,150 c.c. halted by Methergine, 1 c.c. intravenously and 1 c.c. intramuscularly with uterine massage.

Blood loss of 500 c.c. or more was found only in the above five cases for an incidence of 2½ per cent in these 200 cases.

Comparison of our blood loss with reports in the literature may be made by referring to Tables I and II.

TABLE I. COMPARISON OF BLOOD LOSSES REPORTED BY TWENTY DIFFERENT OBSERVERS*

	c.c.		c.c.	
Tarnier	600.0	Brandt	195.0	
Ahlfeld	505.1	Vaux et al.	192.62	(Inhalation)
DeLee	500.0	Jess	187.8	
Williams	343.7	Calkins	179.0	
Plass	317.0	Ryder	177.0	
Tucker	300.0	Leff	171.75	
Fortin	275.0	*Present series*	168.07	(Gross) (Intramuscularly)
Pastore	271.3	*Present series*	113.24	(Gross) (Intravenous)
Calkins	222.0	Arnell	111.0	
Scott	198.7	Vaux et al.	110.75	(Caudal)
		Adair et al.	100.0	

*Many of these reports were estimations and not accurate measurements.

TABLE II. INCIDENCE OF POSTPARTUM HEMORRHAGE (501 TO 600 C.C. OR MORE)

	%		%	
Adair et al.	13.7	Urner	3.4	
Williams	13.0	Vaux and Mitchell	2.8	
Fortin	7.4	Calkins	2.5	
Pastore	7.1	*Present series*	2.5	(Gross)
Pastore	6.4	Brandt	1.25	
Peckham and Kuder	6.14	Polak	0.30	
Tucker and Benaron	4.2	Vaux and Mitchell	0.00	(Caudal)

Comments

1. Methergine, a synthetic ergonovine-like substance, appeared to be nontoxic administered intramuscularly in 100 cases and intravenously in 100 cases.

2. This drug appeared to reduce postpartum blood loss by both methods of administration as compared to other available statistics.

3. When given intravenously immediately after the birth of the infant, the drug produced definitely less blood loss than when given intramuscularly immediately following placental delivery.

4. By the intravenous route, immediately following delivery of the child, the placental delivery is accelerated by about three minutes.

5. Incarceration occurred in the intravenous group in 3 per cent of the cases, but placental removal was easily accomplished under general anesthesia.

Conclusion

We are of the opinion, from this preliminary series of cases, that Methergine is a nontoxic and efficient oxytocic drug.

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DYSTOCIA DUE TO THE SHOULDERS

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DYSTOCIA due to the shoulders occasionally presents a serious problem. This may be due to one or a combination of several factors; with an oversize baby, the shoulders are large in proportion to the head and the anterior shoulder may impinge upon the anterior arch of the pelvis in such a manner as to offer a serious obstacle to delivery. This event may occur unexpectedly, when a large baby is being delivered through a slightly contracted pelvis through which a moderate-sized baby had previously been successfully and easily delivered. The use of analgesics and anesthetics contribute to the difficulty of the situation because they practically eliminate the possibility of cooperative assistance on the part of the patient and minimize the effectiveness of the natural forces.

Faced with a situation of this sort, the writer extemporized the following procedure: With adequate anesthesia the fetal body was allowed to rise into the mother's abdomen as far as it would. The operator's hand was passed in posteriorly to find the posterior arm, and, failing to flex the elbow, the operator's hand was advanced till the fetal wrist could be released from its position across the posterior border of the pelvic inlet. The fetal elbow was then flexed and the hand gradually swept down over the anterior chest. At this point in the procedure the posterior shoulder was out, but the anterior shoulder was still engaged against the symphysis.

To release this anterior shoulder the fetus was rotated approximately 180 degrees (with the help of an assistant) so that the shoulder which was out came into a position just outside the symphysis. This maneuver entirely unlocked the obstruction and the remainder of the delivery was readily completed.

Subsequently the fore part of this procedure was found very nicely presented by DeLee in his textbook, *The Principles and Practice of Obstetrics*, and a similar presentation appears in Titus' work, *The Management of Obstetric Difficulties*. Both of them have stated that after delivery of the posterior shoulder the remainder of the delivery is readily accomplished. This does not appear always to be the case and DeLee's illustration shows the operator's hand making suprapubic pressure to force the anterior shoulder under the symphysis, which might subject the fetal thorax to severe compression. In such a case the lungs are not aerated and are relatively incompressible so that the pressure may be transmitted to the heart, preventing the filling of its chambers, stalling the circulation, and leading very soon to permanent cardiac arrest. The maneuver of rolling the baby over on its longitudinal axis and unlocking the obstruction avoids compression of the thorax, facilitates the delivery, and should prove a useful addition to the procedure.

Since first extemporizing this procedure, several years ago, the writer has had several occasions to resort to the maneuver when the commoner methods failed to complete the delivery.

Fig. 1.—Impaction of the anterior shoulder against the symphysis in the case of an oversize fetus, preventing delivery without damage unless the impaction is decomposed.

Fig. 2.—Pressure with the index finger at the bend of the elbow flexes the arm and brings the wrist within reach. Often the wrist is so pinned against the posterior border of the pelvic inlet by the fetal trunk that the operator must carry his hand higher and release the wrist directly.

Fig. 3.—The fetal forearm is swept down over the front of the fetal chest and the hand brought out.

Fig. 4.—The posterior fetal hand and arm having been brought out, the posterior shoulder rides over the perineum which is crowded back by the arm as it is allowed to hang down. In some cases delivery may follow easily; in others, the impaction of the anterior shoulder against the symphysis is a serious obstacle.

Fig. 5.—To disengage the anterior shoulder, the occiput is grasped with one hand and the posterior shoulder with the other, while an assistant pushes the fetal back over the midline to the other side of the mother's abdomen as the posterior shoulder is brought to the front.

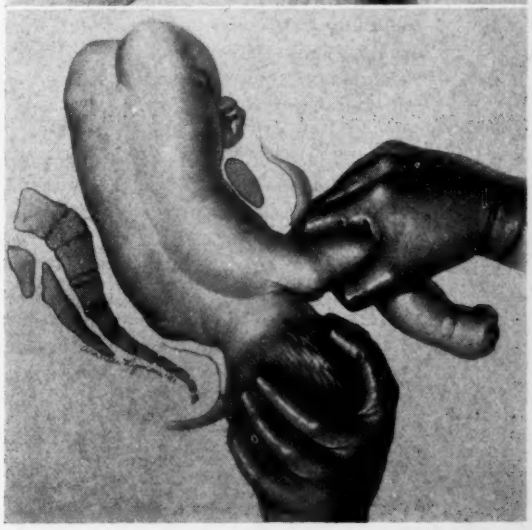

Fig. 6.—Completion of the rotation of the fetus on its long axis with complete release of the impaction of the shoulders.

In these cases delivery was accomplished entirely without injury to mother or baby. Rolling the fetus over, carrying the fetal back over the midline of the mother's abdomen to the side toward which the fetus originally faced, thus completely releasing the anterior shoulder, is the only feature not previously described, to the knowledge of the writer.

SICKLE-CELL ANEMIA COMPLICATED BY PREGNANCY

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(From the Salvation Army Booth Memorial Hospital)

THE number of published cases of sickle-cell anemia complicated by pregnancy is so scarce that the description of another may be justified.

From the literature the author was impressed with the fact that in several cases the nature of the anemia or even the anemia itself, in spite of the prenatal care, were not diagnosed until after the patient's admission to the hospital either because of the onset of labor or of an intercurrent infectious disease. Moreover, in a few unfortunate cases the correct diagnosis was made at the postmortem table only. Inasmuch as the foreknowledge of the existence of this serious ailment may alter the prenatal care and thereby improve the immediate prognosis, greater awareness of this condition and its means of detection may be of considerable practical importance. The author had an opportunity of studying a case of sickle-cell anemia long before term and at close range.

L. S., a 35-year-old nulliparous Negro woman, presented herself with the complaints of amenorrhea of about seven months' duration. The last menstrual period occurred on Oct. 15, 1943. Presently she complained of shortness of breath on slightest exertion, fatigue, and mild pains in the muscles of the thighs, noticeable especially upon locomotion. Her past history revealed that besides the usual childhood diseases such as measles, mumps, chicken pox, and whooping cough, the patient had had typhoid fever at the age of 12 years. When about 14 years old, an anemia of undetermined etiology was diagnosed. In her early teens the patient underwent a tonsillectomy and in her adult life (1938) an appendectomy from which she made an uneventful recovery. Menstruation began at the age of 13 years and was uneventful until the year preceding pregnancy when the intervals between the periods lengthened to six to seven weeks, instead of the usual twenty-eight days. The flow lasted three days and was scanty as usual.

The family history was irrelevant to her present condition. The patient was one of six children. Neither of the parents and none of the siblings had suffered from anemia of any kind. The father was dead, the mother is hypertensive and still living.

As long as the patient could remember she had been troubled with intermittent muscular pains of various intensity. At times the pain was so severe that she had to be confined to bed and strong sedatives were needed to alleviate it. Several groups of muscles usually were involved, namely, those of the thighs, hands, wrists, neck, and abdomen. During these attacks some elevation of temperature occurred, and as high as 103° F. was encountered upon a few occasions. In her early childhood these attacks were considered "growing pains," even when, at the age of 14 years, an associated anemia was discovered. The nature of the anemia was not understood then, but its severity and lack of response to medical management necessitated a blood transfusion. At this period of her life the patient's health was impaired to such an extent that her schooling had to be interrupted for a whole year. The following few years the patient was well enough not only to resume her general education but even to take up nurse's training and to practice her profession successfully. After several years of satisfactory health, the patient, at the age of 20 years, had one of her attacks of muscular pains and the sickle-cell nature of her anemia was diagnosed for the first time. She was treated medically off and on, and during the following ten years the attacks of muscular

pain of various severity intermingled with periods of comparatively fair health. In 1938 the patient was stricken with pneumonia. A week later she developed a typical attack of muscular pain, fever of 102° F., nausea and vomiting. The blood picture at this time showed a red count of 3,000,000 with a leucocyte count of 27,000. The patient under medical treatment improved subjectively, but not objectively, the blood picture remaining unchanged; a few months later the red blood count fell even below 2,000,000 per cubic millimeter. Since 1938 the patient had had, on the average, one or two exacerbations yearly, during which time the sickle-cell nature of her anemia was confirmed on several occasions. In February, 1944, her red blood count fell to the low level of 1,500,000 per cubic millimeter. She needed three blood transfusions in one week to restore her health. At this time a pregnancy of about three and one-half to four months was detected. The onset of the pregnancy was uneventful in every other respect; no vomiting or nausea accompanied it. The presence of albumen was a constant finding in the urine for some time prior to and throughout the pregnancy. Upon admission to the hospital the patient at thirty-two weeks' gestation weighed 109 pounds. She was found to be of small stature (4 feet, 11½ inches) and of slender build. She appeared undernourished and her extremities were especially thin. Her heart was enlarged to the left; the apex beat was felt at the sixth costal interspace. A loud systolic murmur was heard at the apex and base.

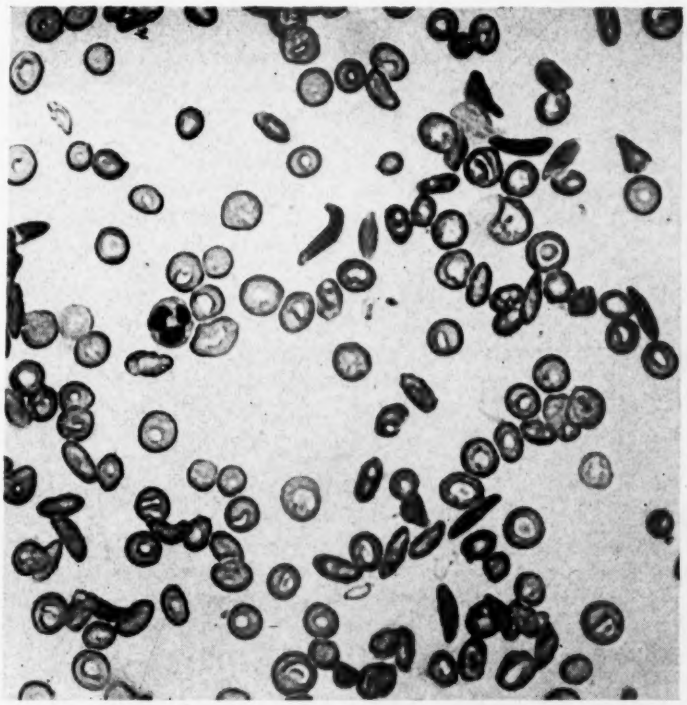

Fig. 1.—A stained preparation of peripheral blood (×540). Note the hyperchromatic elongated and sickle-shaped cells.

A few crepitant râles were heard in the lower portions of both lungs posteriorly. The abdomen was tense due to considerable meteorism, and its wall showed a wide right rectus scar. The spleen and liver were not palpable then. The fetus was in cephalic presentation, and its heart tones were of good quality. The pelvic measurements revealed a generally contracted and funnel-shaped pelvis. Interspinous diameter measured 24 cm., intercristal 25 cm., intertrochanteric 26 cm., Baudelocque 17.5 cm., and the diagonal conjugate 11 cm. The conjugata vera was estimated at 9 cm., the pubic arch at about 80 degrees, and the biischial measured 7½ cm. The vagina was short and narrow, the vulva infantile. The blood pressure upon first examination read 130/90 and the pulse 96. Both sclera showed yellow-brown patches. The laboratory findings were as follows:

Red cell count	3,050,000
White cell count	8,200
Hemoglobin	54 per cent

There were 15 to 20 per cent of sickle cells in the dry smear and 80 per cent in a twenty-four-hour moist preparation. Anisocytosis and polychromasia were detected. Normoblasts were seen in the amount of 97 cells per 100 white blood cells. Howell-Jolly bodies and punctate basophilia were observed. Reticulocytes were increased up to 15 per cent. The platelets were approximately within normal limits, amounting to 210,000 per cubic millimeter.

The differential count of white cells revealed 82 per cent polymorphonuclear cells, of which 8 per cent were stabs and 74 per cent segmented forms. Besides these, 10 per cent were small lymphocytes, 3 per cent large lymphocytes, and 5 per cent monocytes. The bleeding and coagulation time were well within normal range, namely two and one-half and four minutes, respectively. The icteric index of the blood was increased to 29 per cent. The patient was serologically negative and free from Neisserian infection. The blood belonged to group A and contained the Rh factor. A urinalysis revealed the presence of albumen in the amount of 2 Gm. per thousand. Occasional hyaline casts were found microscopically. Blood chemistry showed a nonprotein nitrogen of 27 mg., and 4.3 mg. of uric acid per 100 c.c. of blood.

The patient was hospitalized during most of her stay at the Salvation Army Home. During this time she complained frequently of mild pains in different muscular groups, mostly in those of the extremities. She ran a slight afternoon temperature, ranging from 99 to 100° F.; the most frequent temperature, however, was 99° F.

Upon three occasions the muscular pain was so severe that only morphine sulfate in ¼ grain doses was able to bring her relief. The patient was placed on a high-protein salt-restricted diet. Iron sulfate, 5 grains three times a day, vitamin B complex three times a day, and vitamin C in 50 mg. doses were the oral medication of this time. Despite the treatment and considerable amount of bed rest (the patient was allowed to be out of bed daily for short periods of time), three weeks later the red count fell to 2,400,000 and the hemoglobin remained practically unchanged (55 per cent). On June 27 the patient received 500 c.c. of compatible citrated blood from a donor of the same group and Rh positive. No untoward reactions occurred. A week later the red count rose to 3,400,000 and the hemoglobin to 58 per cent. The patient improved subjectively; she complained of less fatigue and a diminution in muscular pain was noted. On July 7 another blood transfusion was given from a universal donor, the blood being cross-matched. At the conclusion of the transfusion, the patient developed an attack of severe pain in the muscles of the neck and in the epigastrium. Morphine alone was able to bring comfort. The temperature remained normal; chills were not present and the urinary output not diminished. This attack of headache and muscular pain was considered the usual manifestation of her disease and not a reaction from the blood transfusion. After this transfusion the patient improved again, the weakness was less complained of, and the muscular discomfort less pronounced.

On July 11, one week before the expected date, the patient fell into labor. The fetus was in right occipitoposterior presentation. The heart tones were regular, the rate fluctuating between 132 to 140. The head was at the level of the spine, the pains were strong and frequent, but the progress slow. Her blood pressure at the onset of labor was 140/92 and rose to 150/100 at the end of the first stage, which lasted thirty hours. Morphine sulfate, ¼ grain, procured the much-needed rest, and after a second stage of almost three hours the head was still in a posterior position. A midforceps was done after a preliminary left mediolateral episiotomy, and a 5-pound 5½-ounce male infant was extracted with difficulty. The infant was born in good condition and continued to do well throughout its neonatal period. At the age of 3 weeks he showed a red count of 5,310,000 cells, hemoglobin 80 per cent, and a sickle-cell trait. The mother made a good recovery. There was no morbidity according to the accepted standards. The highest temperature was 100.2° F. which occurred once only during the first twenty-four hours following delivery. The unusual feature of the puerperal period was the considerable intestinal distention and acute dilatation of the stomach, occurring on the second day postpartum. Gastric lavage relieved the stomach distention, and prostigmine methylsulfate 1:2,000 given intramuscularly in conjunction with enemas combated the intestinal distention within the following twenty-four hours. Another notable feature of the puerperium was an extremely small amount of lochia, some days almost none. On the ninth day the patient was allowed out of bed. She felt well and continued to do so throughout the period of observation, which ceased at six weeks postpartum. Three weeks after childbirth the blood count revealed 2,900,000 red cells per cubic millimeter and 50 per cent hemoglobin. Anisocytosis and a moderate number of sickle cells were present. The icteric index fell to 16 per cent. Repeated urinalyses throughout her postnatal period continued to show the presence

of 3 plus albumen and occasional hyaline casts. Upon the final examination her general health was found to be better than at any other time since her pregnancy started. The pelvic organs involuted well. The episiotomy healed very well, and the pelvic floor was good. The heart showed the same findings as upon admission. The spleen was not palpable but the liver was felt 3 fingerbreadths below the right costal margin. It is likely that the enlarged liver was not palpable during pregnancy due to tenseness of the abdomen. The patient left the hospital for her home state in good condition. She has been heard from since as being employed and enjoying fair health (first week of January, 1945).

Discussion

Sickle-cell anemia since its description in 1910 by Herrick is a well-known clinical entity. According to the literature it is a familial and hereditary disease, the sickle-cell trait being transmitted according to the Mendelian law as a dominant factor. The clinical picture is so characteristic that once the condition is suspected it is easily diagnosed. If one keeps in mind the salient features of this ailment, such as attacks of muscular and joint pain, weakness, elevation of temperature in the presence of anemia, one is likely to arrive at a correct diagnosis. Of late, proper emphasis has been placed upon the frequency of secondary anemias, occurring in pregnancies, and a routine blood count is advocated for their detection. Should an anemia thus found be associated with a history of attacks of muscular and joint pains, then a suspicion of sickle-cell anemia should arise, and the diagnosis either be confirmed or refuted by complete blood study of fixed and moist preparations. This is especially true when the patient is a Negro because of the susceptibility of this race to the ailment.

The association of sickle-cell anemia with pregnancy is not frequently met with; only 17 cases have been described thus far. Kobak and associates (1941) analyzed and summarized the literature upon this subject. In the series collected by them from the literature, the average age of those afflicted with this blood dyscrasia is 22.4 years, the oldest patient being 30 years old. It is a known fact that this condition has a predilection for the young; its incidence progressively decreases as the age increases. No case has been recorded in a patient over 30 years of age (Sydenstricker, 1930). It is believed by some (Sodeman and Burch, 1937) that fertility is impaired in those suffering from this type of anemia. According to several observers pregnancy exercises an unfavorable course upon the disease and the mortality among the patients is high. About 33 per cent of the reported pregnant cases died during pregnancy, labor, or puerperium (Kobak). No specific treatment is known to exist; the response to medication is unsatisfactory. Blood transfusions improve the patient's condition temporarily at least. Patients are very susceptible to infectious diseases to which they finally succumb. A few patients were described who died not from infection but during an abdominal crisis, the cause of which was not definitely known, but which was probably due to infarction occurring in some abdominal viscus (Yater and Mollari, 1931). As far as the author can judge from the literature, the 35-year-old patient here described is the only one among the sufferers of sickle-cell anemia to reach this age; the oldest among the previous reported cases have not exceeded the age of 30 years. It is likely also that the duration of the anemia is the longest among those thus far described. It is definitely known that the sickle-cell nature of her anemia was diagnosed fifteen years ago, but it is probable that the anemia of her childhood was a manifestation of the same condition. In spite of the impaired general health, the hypomenorrhea and oligomenorrhea, the patient, an unmarried woman, readily conceived just a few weeks after sex relations were commenced and practiced in modera-

tion. Thus, seemingly, her fertility was not affected adversely, in contrast to the view of those who hold that such is the case with other patients. It appears from the study of this case that pregnancy does aggravate the condition of the patient's anemia. During the long span of her anemia, only in the beginning of the pregnancy did the red blood count reach its lowest ebb of 1,500,000 per cubic millimeter.

Unlike the majority of other patients with sickle-cell anemia, this one, fortunately, did not run a febrile puerperal course in spite of the prolonged labor and operative delivery. This, in part, is possibly due to the fact, as the author would like to believe, that the patient was well prepared for her ordeal by repeated blood transfusions, given not as an emergency measure during a crisis but prophylactically as part of the antenatal care and at the onset of labor.

Just as it is essential to treat medically the secondary anemias of pregnancy in order to build up the resistance of the patient and thus enable her to meet the exigencies of a difficult delivery or a postpartum hemorrhage, the occurrence of which cannot be foretold beforehand, so much more important, even imperative, is it to prepare the sickle-cell anemia patient for her ordeal with the only effective means at our disposal, namely, the supply of normal blood. True enough as expected, the blood transfusions do not cure the pregnant patient and do not alter the unfavorable prognosis. But if by administration of blood the patient can be carried through this difficult and potentially dangerous period of her life with greater safety, then the blood transfusions must be regarded as of paramount importance in the care of such patients.

Even though the success achieved is temporary and the inevitable outcome is only delayed, the obstetrician may consider his task well accomplished for the time being. Only further progress in the knowledge of this dyscrasia and its causes may render its treatment more specific and the prognosis more favorable.

I wish to express my gratitude to Dr. H. Sweeny of the Municipal Tuberculosis Sanitarium Laboratories for the various and numerous tests performed with unfailing courtesy by his technical staff of assistants. Without his cooperation the study of this case would have been impossible.

I am also greatly indebted to Dr. I. Davidsohn, the Director of the Laboratories of the Mount Sinai Hospital of Chicago, for his help in the study of the Rh factor of the patient and the compatibility of her blood with that of the prospective donors.

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CONGENITAL ABSENCE OF THE SACRUM AND COCCYX COMPLICATING PREGNANCY

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UNUSUAL pelvic abnormalities during pregnancy are important from the point of view of management during labor. These abnormalities have become more important in recent years with the more common usage of roentgen pelvimetry. Many unsuspected abnormalities have been discovered by this important method of examination, and this has undoubtedly reduced the incidence of so-called difficult labor. The use of the x-ray in borderline cases and in cases of unexpected bony abnormality is therefore of extreme benefit to the obstetrician. The following case presents a rare congenital abnormality of the pelvis in which there was a total absence of the sacrum and coccyx. This is visualized in the x-rays, Figs. 1 and 2. In addition to this bony abnormality, this case presents certain urologic complications as manifested by a total incontinence of urine due to a lack of sphincter control. The following case history is presented:

A 20-year-old white primipara was first seen in the prenatal clinic when she was approximately sixteen weeks pregnant. Her estimated date of confinement was Sept. 26, 1942. Her prenatal course and past history were relatively uneventful except for her skeletal development. She was aware of having a skeletal anomaly but was not aware of its extent. She also gave a history of being incontinent and partially involuntary, although she had some tone to her rectal sphincter muscles. She had been seen by numerous physicians and it was at one time suggested that she have a ureteral implantation into the large bowel for congenital incontinence. She refused this operation at the time. The patient stated that she used from six to eight dozen sanitary napkins daily and always wore baby rubber pants because of her bladder difficulty. Her family history was negative with reference to any etiological agent in the patient's condition. The patient was of short stature (5 feet 1 inch in height) with a broad (masculine) type of shoulder girdle. She had thick pectoral and deltoid muscles in comparison to those of the rest of her body. Her vertebral column was straight and terminated at the junction of the last lumbar vertebra and the pelvic girdle. There were two marked depressions at the site of the posterior superior spines of the ilium. There was almost a complete absence of the intergluteal fold, and the subcutaneous tissue and muscle formed a partially loose apron over what would normally be the sacrum. Although there was some tone to the rectal sphincter, there was no difficulty in inserting two fingers into the rectum without much discomfort to the patient. There was a moderate atrophy of the thigh muscles and a marked atrophy of the muscles of the leg and foot. The patient had a waddling gait, but there was no evidence of unsteadiness on walking. There was no loss of sensation to touch or temperature below the umbilicus, and there was no loss of motor function. X-ray of the pelvis at term showed a single fetus with the back to the left and the small parts to the right (Fig. 3). The head was above the pelvic inlet and ballotable on palpation above the brim of the pelvis. The head appeared to be full term in size. The pelvic inlet was asymmetrical and did not correspond to any of the pure types of pelves described either by the Thoms or Caldwell-Moloy classification. It appeared cylindrical in appearance with the greatest diameter of the cylinder running anteroposteriorly. The head seemed to be too large for the pelvic inlet and could not be pushed into the inlet by manipulation over the brim of the pelvis. A diagnosis of relative cephalopelvic disproportion was made and it was deemed advisable to give the patient a test of labor. She was admitted to the hospital on Nov. 11, 1942, and the following day she was given 1 minim of pitocin. Following this injection she had hard contractions which came every four to six minutes and lasted forty to fifty seconds. The patient made no progress. Since she showed no other abnormalities with reference to the pregnancy itself, it was deemed advisable to continue with the test of labor. She had some contractions all through that night and the following day the contractions became more severe and more frequent. Still she made no progress and it was decided at this time to interfere.

Fig. 1.—Lateral view of the pelvic girdle showing the absence of the sacrum and coccyx. There is some sacralization of the last lumbar vertebra.

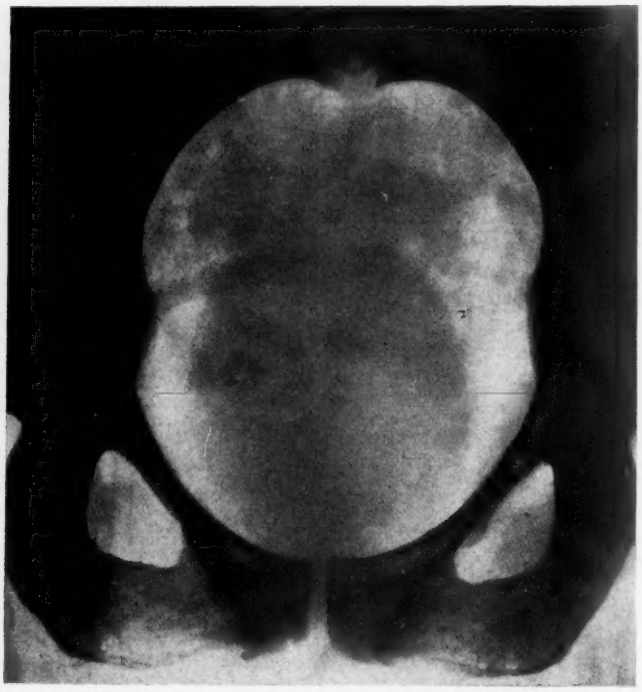

Fig. 2.—Anteroposterior view of the pelvis showing the absence of sacrum and coccyx.

Under spinal anesthesia a low classical cesarean section was done and a living infant was delivered that gave a spontaneous cry and respiration. The infant stopped breathing shortly thereafter and failed to respond after several attempts at resuscitation. Autopsy revealed that the baby had a congenital heart lesion and a complete atelectasis of all lobes of the lungs. X-ray of the baby's spine failed to reveal any abnormality of the bony structure. The patient had an uneventful postoperative course and was discharged from the hospital in good condition. Her urinary difficulty continued, however, and she was readmitted for surgical treatment of her incontinence. On Jan. 6, 1944, under general anesthesia, a combined vaginal and abdominal operation was done for relief of her incontinence. A cystocele repair was done and two portions of the sheath of the rectus abdominis muscles were brought under the bladder for support according to the method described by Aldridge.[1] There was no immediate relief from the procedure, but within a period of three months the patient experienced a desire to urinate which was something she had never enjoyed previously. However, she was still unable to hold her urine and would usually expel it spontaneously before reaching the lavatory. This has since improved somewhat but not to any great extent. This patient is now again pregnant and time will tell what the effects will be on the operation for urinary incontinence. At the present writing no change has occurred over that of her prepregnancy status.

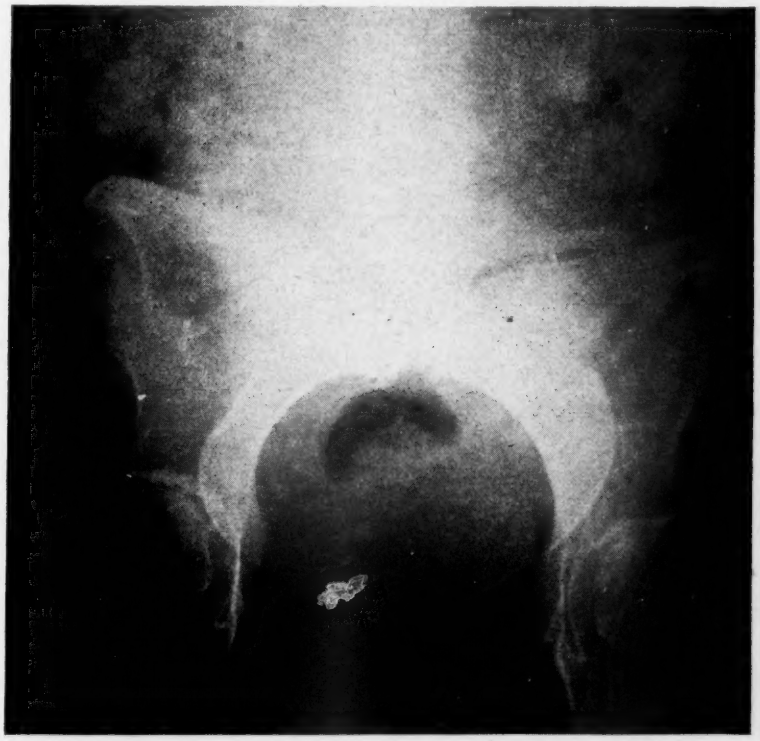

Fig. 3.—Anteroposterior view of the lower abdomen and pelvis showing configuration of the pelvic inlet and the fetal head riding above the inlet.

This is an extremely rare anomaly of the pelvis. Aldridge[1] reports in his article on urinary stress incontinence that procedure similar to this was used on a girl operated upon by Price.[2] The latter's patient was a young Chinese girl who came for help because of incontinence of urine and feces due to a lack of sphincter innervation. She was operated on at 16 years of age. She had two operations with good results. Although this girl had incontinence of urine primarily, she also had a congenital absence of the sacrum and coccyx, which undoubtedly accounts for this incontinence. Price gives no reference to any other cases similar to this abnormality.

In the case here presented the uterus responded to labor like any other normal uterus. Contractions were regular and of sufficient strength to require the use of some analgesia. The cervix dilated but there was no descent of the head. It was felt that a test of labor would indicate whether the head would

pass the widest diameter of the pelvic inlet, but due to the absolute disproportion between the fetal head and the pelvic inlet, there was not the slightest sign of any descent. There is much encouragement to be offered by the procedure outlined by Aldridge for the cure of urinary stress incontinence. Although used by him for cystoceles that did not respond to other more simple types of repair, it has been of definite advantage to this patient. It is problematical what the present pregnancy will do to the plastic repair done one year previously.

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STRANGULATED HERNIA CONTAINING PREGNANT UTERUS AT TERM

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THE importance of hernia as related to pregnancy is perhaps not sufficiently understood because of its infrequent occurrence. It does, however, occasionally become a real obstetric problem, and this is particularly true when most or all of the pregnant uterus has become strangulated in a hernial sac. In the earlier months, the pregnancy is often terminated by either spontaneous or therapeutic abortion. Even when the gestation continues to or near term, the termination may be spontaneous or by means of forceps through the natural passages, and a living child obtained. But when the uterus at or near term becomes strangulated, the seriousness of the condition is greatly increased.

Cases of strangulated hernia containing a pregnant uterus at or near term are rare. In an exhaustive search of medical literature only five case reports were found.

Manley[1] quotes Nocolaus Pol, 1531, an Italian physician who "removed a mature infant from a labial hernia." The mother died five days later but the infant survived. Bardeleben[2] demonstrated before a convention in Berlin, December, 1911, a case of pregnancy occurring soon after a pelvic laparotomy where the operative wound had broken down. This was followed by a hernia. At the time of the demonstration the gestation was in the eighth month and healed abdominal walls were "thin as paper." The author advised waiting until term; then, if difficulty presented itself in a spontaneous delivery, a section should be performed. No report later as to outcome. Typyakov[3] reported the case of a woman, 23 years old, who was five months pregnant with the uterus strangulated in a subumbilical hernia. She developed severe abdominal pain which suggested that an abortion was likely, and an operation was advised. The hernial ring was incised, the uterus replaced in the abdomen and the hernia repaired. The patient recovered, went to term, and had a normal delivery. Cartaya[4] reported a case in which a uterus the size of a four and one-half months' pregnancy became strangulated in an incisional hernia. Severe abdominal pain and vomiting ensued. Mechanical attempts at reduction failed and operation was advised. As in the case of Typyakov, the constricting ring was cut, the pregnant uterus returned to the abdominal cavity, and the hernia repaired. The patient went to term and had a normal delivery.

The most typical case was reported by Rosner.[5] The patient was 30 years old and had had four pregnancies, the last one six years before. A subumbilical hernia had been present for two years before the present pregnancy. Abdominal pains developed at six months' gestation and operation was advised, but it was refused. Nothing more was heard of this patient until she was at term. She then developed severe pains which continued for forty-eight hours,

when it was determined that the pregnant uterus was entirely irreducible. Cesarean section was advised, but after opening the abdomen a Porro operation was decided upon and carried out. The mother recovered without complication but the infant died on the day of delivery from what was diagnosed clinically as congenital heart disease. An autopsy was not performed.

Because of the apparent rarity of this condition the following case is reported.

Case Report

Mrs. A. M., a white married woman, aged 37 years, was a para xi at term and had been in unusually severe labor for fourteen hours without measurable progress when first seen by the writer. She had had a supraumbilical hernia for several years which had been the cause of considerable trouble in three previous labors and especially with the last one, about eighteen months before the present delivery. Previous deliveries, however, ultimately were accomplished without interference, except the use of a tight abdominal binder during labor.

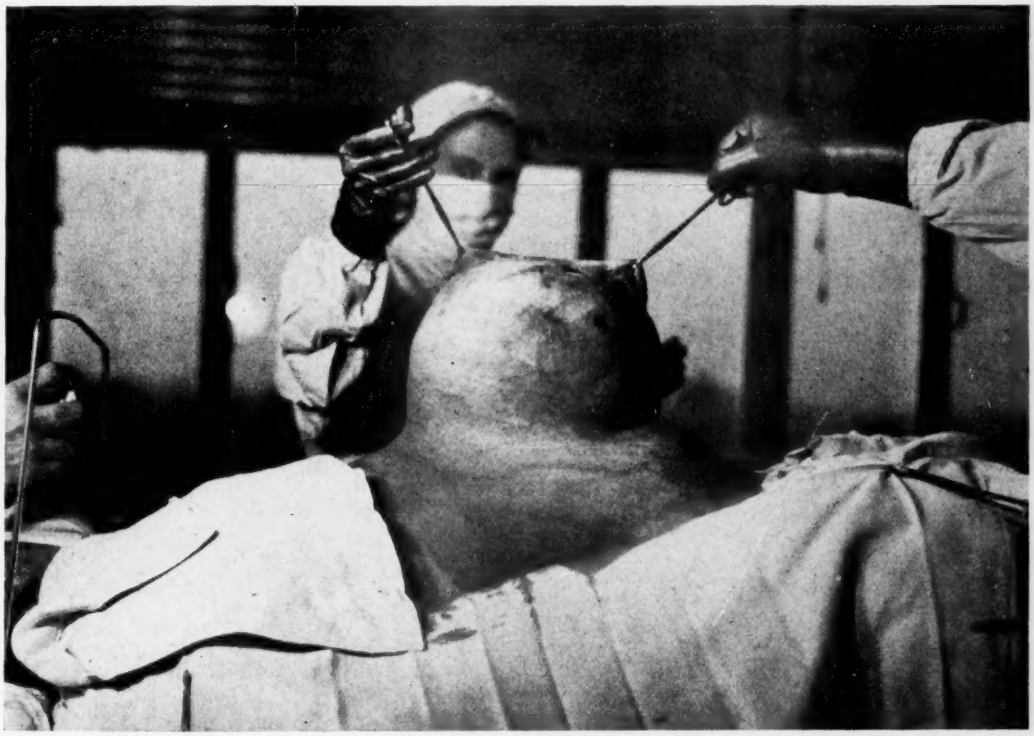

Fig. 1.—Strangulated hernia containing pregnant uterus at term. (Author's case.)

Examination showed the patient to be a woman of average size and nutrition. From the upper abdomen a tumor was observed apparently protruding through a median cleft in the abdominal wall above the umbilicus. Between pains the mass extended 17 cm. above the normal curve of the abdomen, and during pains it was about 7 cm. higher still. Ulcers each about 4 cm. in diameter were present in the overlying skin, due to irritation from adhesive straps which had been used unsuccessfully by the patient to control the hernia. Enormous varicosities were present in both lower extremities, but no palpable thromboses were found. Blood pressure was 140/90, pulse 88, temperature 97.8° F., and respirations 22. Urine was normal. Blood: red blood cells 3,540,000, white blood cells 10,900, hemoglobin 8.8 Gm., color index 0.78, and blood type 4. X-ray examination disclosed a full-term fetus with head not engaged. The uterine contractions recurred at from three- to five-minute intervals and were unusually violent, due partly to the strangulation. Rectal examination failed to reveal any fetal presenting part, nor any effacement or dilatation of the cervix, which was very high. Vaginal examination was not made, but no vaginal bleeding was evident. A diagnosis of strangulated abdominal (supraumbilical) hernia, with incarcerated pregnant uterus at term,

was made. Mechanical attempts to reduce the hernia were futile, and cesarean section was carried out at once.

After excising a considerable amount of skin to eliminate the infective cutaneous ulcers, the tumor was well exposed and found to consist of the entire fundus and about half of the corpus with enormously varicosed broad ligaments. Reduction of the mass was impossible without enlarging the already large fascial ring with resulting increased difficulty of hernial repair. A classical section was performed because the lower uterine segment was unapproachable without enlarging the ring.

On incising the corpus, a large placenta was found immediately underneath. The buttocks and both lower extremities of the fetus were incarcerated immediately under the placenta. Of necessity the placenta was quickly removed first, followed by the fetus as a breech presentation. The amount of bleeding was not unusual, and the baby cried lustily almost at once. The infant, a girl, weighed 10 pounds and 14 ounces.

The uterine incision was sutured with four layers of No. 1 chromic catgut, and on account of its diminished size, the uterus became easily reducible. The surplus tissue of the hernial sac was excised, the peritoneum sutured, and the fascia closed by imbrication, using catgut sutures. Silkworm-gut was used for retention sutures and Nylon for the skin.

There was some breaking down of the superficial part of the wound by the tenth day and the hernioplasty was only partially successful; yet enough so, that eighteen months after the operation, the patient delivered a twelfth baby weighing 8½ pounds, following a three-hour labor, without incident.

A mild degree of thrombosis in the superficial veins developed a few days after operation in the left and then in the right popliteal regions. These were painful and tender and attended with a moderate degree of swelling of the lower extremities, but the condition had largely subsided when the patient left the hospital on the twenty-fourth postoperative day.

The baby had an entirely normal postdelivery course.

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GAS BACILLUS INFECTION OF THE UTERUS TREATED WITH PENICILLIN

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THE gas bacillus is widely distributed in nature. It is a normal inhabitant of the intestinal tract of man and is found in the vagina of 4½ to 8 per cent of pregnant women.[1, 6, 7] Falls[2] recovered the organism from the blood stream of a puerpera who had no symptoms of infection. Not only is the *Clostridium welchii* well-nigh everywhere but it is a spore-bearing organism that withstands boiling and is resistant to ordinary measures of sterilization. Rendle-Short[3] believes that the pubic hairs become contaminated by feces, whence the germs are introduced into the vagina by the examining finger. In view of these facts it is difficult to explain why infection with this bacterium is not more common than it is. We have seen only three proved cases and one suspicious case in a combined experience of forty-five years. The latter was seen by the senior author a number of years ago. A Negro woman, who was admitted to St. Philip Hospital after an abortion, died in a few hours with symptoms strongly suggestive of gas bacillus infection. The uterus crepitated after death, but at autopsy only the colon bacillus was found.

Varying pathogenicity is one explanation that is advanced to explain the infrequency of genital tract infection. Usually the organism needs dead or devitalized tissue in which to get a start. Once it gets a start and builds up virulence, it produces a profound and usually a rapidly fatal illness. As would be expected, infection with the Welch bacillus is more frequent with abortions than with full-term deliveries. There is more trauma connected with induced abortions and usually the fetus dies before it is expelled. With term or near-term deliveries, placenta previa may be a predisposing factor. Two fatal cases of placenta previa treated with Willet's forceps have recently been reported in England.[8]

Criminal abortions furnish ideal conditions for this type of infection. In the first place the unscrupulous operator is not likely to be scrupulously clean. In the second place, he or she repeats the instrumentation until results are obtained, i.e., the death of the fetus. After the uterine cavity is infected and the fetus is killed, the patient is left to shift for herself. In all our cases, the patients entered the hospital with pubic hair intact. What other breaches of technique had been committed we had no way of knowing. However, not all gas bacillus infections occur in criminal abortions. Sandusk and Manahan[5] report a case in which a therapeutic abortion for severe anemia was done at the Johns Hopkins Hospital.

Russell and Roach,[4] who reported 17 cases, divided them clinically into three groups. When the infection is limited to the fetus and endometrium, with or without physometra, there are no characteristic symptoms. The diagnosis is made by either blood culture or uterine culture. They had six such cases with no maternal death. When the uterine wall is invaded, uterine pain with circulatory collapse is the outstanding symptom. There may or may not be crepitation upon manipulation of the uterus. They had four such cases with three maternal deaths. In one case, gas in the uterine cavity and in the uterine wall was demonstrated by x-ray. In the third group, the blood stream is invaded. There are a chill at onset, nausea and vomiting, jaundice, severe headache, and intense abdominal pain. The urine is often coffee-colored and there are cyanosis and shock. The fatal cases have gas in the lochia. Russell and Roach had seven such cases with six deaths.

The diagnosis depends upon demonstrating the organisms either in blood cultures or in cultures from the uterus. It should be suspected in any severe and rapidly progressive infection, especially if there is evidence of gas formation. This suspicion is heightened when an abortion has been induced outside of a hospital.

The course of the disease is frequently so rapid that no time should be lost in beginning treatment. The patient may die within sixteen hours from the time of the interference. All our cases support the thesis that treatment must be started early.

On Oct. 28, 1941, a 23-year-old unmarried Negro multipara was admitted to St. Philip Hospital with the history of having fallen on her right side the day before. Her last menstrual period began on July 15, 1941. There was no history of an attempted abortion. She looked sick and terrified. There was a trickle of blood-tinged watery fluid from the vagina. Her temperature was 103.4° F., pulse 122, respiration 44, blood pressure 100/60. The fundus was 23 cm. above the pubis and some crepitation was felt about the fundus. Hemoglobin was 76 per cent; red blood cells, 4,260,000; white blood cells, 8,600; polymorphonuclear leucocytes, 86 per cent. She was catheterized but no urine was obtained. Possible diagnosis included: premature separation of the placenta, ruptured uterus, infected abortion with pregnancy of six months. X-ray of chest showed nothing abnormal except the suggestion of free air under the right diaphragm. This suggested a ruptured viscus to one examiner. Six hours after admission to the hospital she suddenly became restless with rapid breathing, and died.

At autopsy the following afternoon, the body was bloated beyond recognition. Gas welled from all tissues and the viscera were all necrotic. The uterus was filled with gas and its inner surface was almost black in color and covered by a rough, shaggy exudate. No cervix was distinguishable. There were no uterine contents. Culture of intraperitoneal fluid showed *Cl. welchii*.

On Jan. 18, 1944, a 17-year-old unmarried white girl was admitted unconscious to the Johnston-Willis Hospital. Her temperature was 101° F. and she looked to be at term. A rectal examination was made and there was an explosive escape of gas from the vagina. In several hours she expelled a six-month macerated fetus and died before the placenta was delivered. Her stay in the hospital was less than twelve hours. Her treatment besides delivery care consisted of a blood transfusion.

It was evident that only a miracle drug could have saved these patients. Penicillin was not available at the time. Theoretically, it is the drug for the purpose because it is effective not only against *Cl. welchii* but also against many of the organisms that are so frequently associated with it in postabortal infections. In case of wound infections, penicillin has been found to be effective against gas bacilli in the blood stream but has no effect upon the bacilli growing in dead tissue. Débridement is as necessary when penicillin is used as it was formerly. By the same token, treatment of postabortal and postpartum infections with penicillin should be combined with local treatment.

Case Report

The patient, admitted to the Johnston-Willis Hospital, Nov. 25, 1944, was 29 years old, white, single, height 5 feet 7½ inches, weight 196 pounds. She said she had had nephritis at 8 years of age, but otherwise had been in good health until the present illness. Her menses had been regular until August 24 to 28. There had been no bleeding since until the day before admission. She had had some nausea and vomiting earlier, and had some headache and edema of her feet. For the past eleven days an unnamed woman had injected soapsuds for the purpose of producing abortion. She had had some abdominal cramping and pinkish vaginal discharge three days before admission. The day before admission bleeding became more profuse and she passed some clots.

Because of a high fever (103° F.) on November 25, she called for medical aid and was admitted ambulatory to the hospital.

On admission she did not appear ill except for having labor pains; temperature was 99.8° F., pulse 86, blood pressure 112/98. At 12:45 P.M., while in bed, she aborted a fetus 20 cm. long with its placenta intact. There was no excessive bleeding. She was given sulfathiazole, 7½ grains every four hours, although her temperature came down to normal the same day. Urinalysis was negative; hemoglobin, 85 per cent; white blood cells, 35,400; polymorphonuclear leucocytes, 92 per cent.

The following day, November 26, the sulfathiazole was discontinued because she had some vomiting and said a doctor had told her she could not take sulfa drugs. At 9:30 P.M. she was found to be in profound shock with cold clammy skin, pulse 110, thready; blood pressure unobtainable. There was no visible bleeding. She was given intravenous glucose in saline, 2 ampules of Cortate, and the foot of her bed was raised.

The next morning (November 27) her temperature was 98° F., pulse 88, blood pressure 92/?. The uterus was hard, tender, about the level of the umbilicus. She did not void that day. A little urine was obtained by catheter. It had a specific gravity of 1.030 and showed a trace of albumin. Red blood cells 5.49 million; hemoglobin 100 per cent; white blood cells, 41,450. A blood culture was taken for *Cl. welchii* which proved negative. She could take only small amounts of fluid by mouth and was fed glucose intravenously. Penicillin was begun; 20,000 units every three hours intramuscularly. She required morphine for pain which appeared to be increasing.

On the third day (November 28) the red blood count was 6.36 million; hemoglobin, 135 per cent; white blood cells, 40,000; polymorphonuclear leucocytes, 90 per cent. She still did not void, but began to void the next day. Her temperature rose to 99.4° F.; then in the succeeding days became subnormal, being as low as 96° F. on the fourth and fifth days post abortal. This was puzzling as she appeared very ill. Her pulse on the fourth day rose to 140, then subsided to 90. At times during this period, she would moan for hours with pain, her uterus being exquisitely tender, as were also the flanks to a lesser extent. The uterus was slightly higher in the abdomen. She still took only fluids by mouth. On the sixth day a flat x-ray of her abdomen failed to show gas in the uterus.

She gradually became more comfortable, and on the ninth day post abortal the penicillin was discontinued, although she still had some generalized abdominal pain. Her uterus was felt 2 fingerbreadths below the level of the umbilicus and was moderately tender. Three blood cultures had been negative, but a culture from the cervix indicated the presence of *Cl. welchii*.

On the tenth day (December 5) she became markedly worse; her temperature was 100° F. She had severe constant abdominal pain and the uterus appeared to be enlarging; red blood cells, 3.58 million; hemoglobin, 75 per cent; white blood cells, 14,950; polymorphonuclear leucocytes, 89 per cent. A fourth blood culture was taken which proved negative. She was restarted on penicillin, 20,000 units every three hours intramuscularly, and given sulfadiazine, 30 grains, for a first dose, then 15 grains every four hours by mouth. She was also given an intrauterine douche of zinc peroxide paste of which almost 5 ounces entered the uterus. The foot of the bed was elevated during this procedure and remained so for one-half hour.

During the next two days (December 6 and 7) she became more comfortable and her temperature was no higher than 99.4° F. Her uterus shrank to halfway between the umbilicus and pubis. On the twelfth day (December 7) the intrauterine douche was repeated but only 1 to 2 ounces would enter the uterus. On the thirteenth day (December 8) the penicillin was discontinued. On the fourteenth day (December 9) she had some nausea and vomiting. The sulfadiazine level had gone from 9.8 on the eleventh day to 13.3 on the fourteenth day. The dosage was then reduced.

On the seventeenth day post abortal (December 12) she developed symptoms typical of a gall-bladder attack with pain and tenderness under the right costal margin, associated with nausea and vomiting. Morphine was required to relieve the pain. On the eighteenth day (December 13) her temperature rose to 101.6° F. A catheterized urine specimen showed acid reaction and a trace of albumin, and 35 to 40 white blood cells per high-power field with clumps of pus cells; red blood cells, 3.16 million; hemoglobin, 68 per cent; white blood cells, 19,750; icteric index, 53. The medical consultant (Dr. T. D. Davis) considered the attack to be a hepatitis, possibly incident to sulfonamide therapy. Her uterus was scarcely palpable and not tender, and it was thought that her hepatitis had nothing to do with her initial infection. However, she was given penicillin, 20,000 units intramuscularly, from the eighteenth to the twenty-first day. She gradually improved and was discharged well on December 22, twenty-nine days post abortion.

Summary

A case of postabortal infection with *Clostridium welchii* is reported, in which treatment with penicillin apparently confined the infection to the uterus. However, it had no effect upon the process within that organ. The uterus continued to enlarge and was exquisitely tender until the patient was given, in addition, sulfadiazine, and local treatment with zinc peroxide. Recovery was then uneventful except for an attack of hepatitis on the seventeenth and eighteenth postabortal days. Our thanks are due to Dr. T. D. Davis for this valuable advice in outlining the treatment in this case.

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OVARIAN PREGNANCY

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BECAUSE of its comparative rarity, ovarian pregnancy is of great interest. The number of proved reported cases is still small, therefore reports of a single case may be recorded.

The case which we present is that of a 26-year-old white woman, admitted on Nov. 14, 1944, with the diagnosis of ruptured ectopic pregnancy. The patient had been well until that morning when she was suddenly seized with severe sharp pain in the region just to the left of the umbilicus. There was no nausea or vomiting associated with the pain. A vaginal discharge was present and described to be thick and tenacious. Menses had always been irregular as to time of occurrence and duration. Her last menstruation was on Oct. 5, 1944, at which time she bled for four days. The previous menses occurred on Sept. 15, 1944. The November period did not take place and there was no spotting or brownish discharge as far as the patient could ascertain.

Blood studies on admission showed a red blood count of 4,570,000, white blood cells 17,600, with 80 per cent hemoglobin. Urinalysis: specific gravity, 1.022; reaction, acid; sugar, negative; albumin, faint trace. Microscopic examination of urine, essentially negative. Blood chemistry: blood suger, 118; nonprotein nitrogen, 31. Serology was negative.

Physical examination revealed a thin woman in acute distress. Blood pressure, 132/60; pulse rate, 100. Heart and lungs were essentially negative. Inspection of the abdomen revealed a slight elevation just to the left of the umbilicus. The patient's legs were drawn upward in an effort to relieve the pain. On palpation, there was marked tenderness about the umbilicus, and a mass about the size of a lemon could be felt in this area. Dullness was percussed in both flanks.

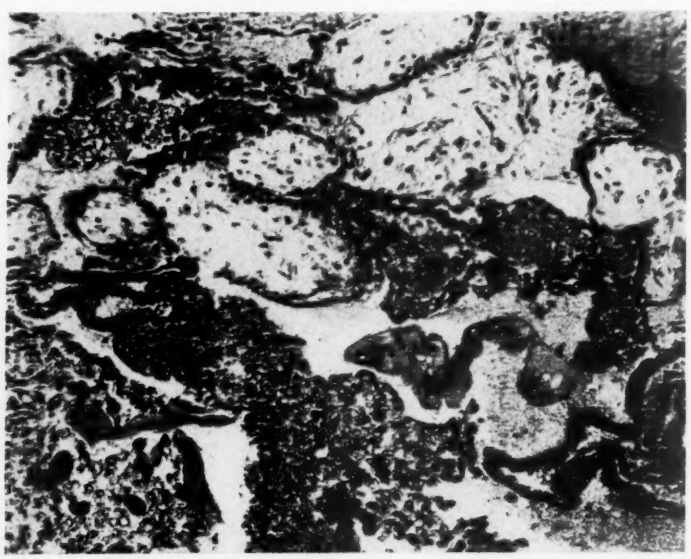

Fig. 1.—Section of white tissue found in blood clot, showing presence of fetal villi and Langhans's and syncytial cell masses.

Pelvic Examination.—The external genitalia were normal; no glands were palpated. The cervix was extremely soft and deviated to the left vaginal wall. The fundus of the uterus was pushed to the right. The right adenexa were normal. The left adenexa presented a small tumor in the region of the left ovary which confirmed the abdominal palpation. It

is interesting to note that during pelvic examination the patient experienced for the first time a burning pain in the left shoulder coupled with shortness of breath and pain on breathing.

Following examination, laparotomy was decided upon. A low midline incision was made under gas-oxygen-ether anesthesia. Upon opening the abdominal cavity, a considerable amount of free blood was found. This was immediately suctioned from the cavity. The pelvic organs as well as the abdominal organs were explored. The right tube and ovary were normal; the left ovary was enlarged with evidence of hemorrhage on its medial aspect. It was connected with the uterus by the ovarian ligament. The tube was entirely discrete from the ovary. The surface of the tube was smooth and not injected. Its fimbriated end was normal in every detail. Since the tube was normal, it was not removed. The meso-ovarium vessels were then doubly ligated and the ovary removed.

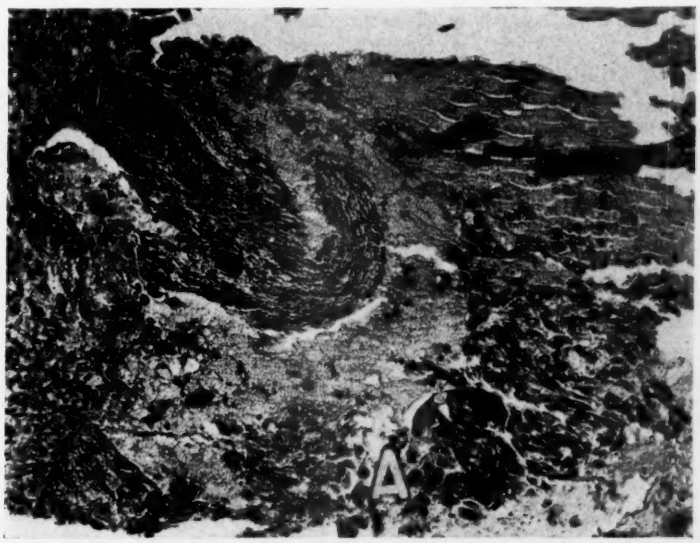

Fig. 2.—Section through ovary showing presence of syncytial and Langhans's cells (*A*) in contiguity with ovarian tissue.

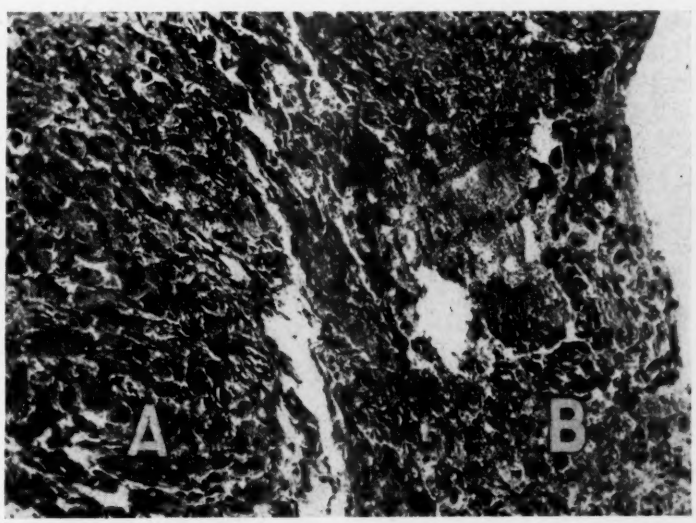

Fig. 3.—Section showing presence of a group of Langhans's cells (*B*) adjacent to a portion of the corpus luteum (*A*).

Histologic Examination.—The gross specimen consisted of an ovary which measured 4 by 5 by 1 cm. It was covered with blood clots and contained at one point a red mass measuring 1 cm. in diameter. Scattered within the clots were fragments of white tissue. Microscopically, sections through the white mass revealed fragments of placental tissue (Fig. 1).

Examination of a section of the ovary showed a defect on the surface which was lined in part by an accumulation of large irregular cells containing large irregular nuclei. These cells resembled syncytial cells (Fig. 2). There was no distinct boundary between these masses of cells and the adjacent ovarian tissue. Another section of the ovary presented a large intact corpus luteum. Here again, there were seen within the adjacent tissue groups of cells which resembled Langhan's cells (Fig. 3). Some few resembled syncytial cells. Some hemorrhagic extravasation was present in the adjacent tissue.

Pathologic Diagnosis.—(1) Ruptured ovarian pregnancy; (2) corpus luteum of pregnancy.

Comment

The case just described seems to fulfill the criteria set up by Spiegelberg. There are some authorities on the subject of ovarian pregnancy who think that serial section of the salpinx must be examined microscopically to distinguish between a primary and secondary ovarian pregnancy. In our case the Fallopian tube was not removed. Since the tube was not edematous or injected and, most important of all, was in no way connected with the ovary, it was decided to leave the tube in situ. Because of this gross observation, together with the pathologic findings described above, we feel that this case is one of primary ovarian pregnancy.

Necrology

RAYMOND EDWARD WATKINS, M.D., a member of the Advisory Editorial Board, died Tuesday, Aug. 7, 1945, of a coronary seizure. Born in 1882, he graduated from the University of Illinois College of Medicine in 1909. Long prominent as a teacher and practitioner of the specialty in the Pacific Northwest, he headed the Department of Obstetrics and Gynecology of the University of Oregon Medical School for many years. Dr. Watkins was a member of the American Gynecological Society, the Pacific Coast Surgical Association, the Pacific Coast Society of Obstetrics and Gynecology, and the American College of Surgeons.

J. K. B. E. SEEGAR, M.D., well-known gynecologist and obstetrician of Baltimore, Maryland, died there Aug. 24, 1945, at the age of 70. He was a graduate of the University of Maryland, in practice since 1900, a member of the Medical and Surgical Faculty, the American College of Surgeons, and of the staffs of the Bon Secours and St. Agnes Hospitals.

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Rebbeck, E. W.: Ultraviolet Irradiation of Autotransfused Blood in the Treatment of Postabortional Sepsis, Am. J. Surg. 55: 476, 1942.

Treatment by autotransfusion of irradiated blood consists in the withdrawal of a predetermined quantity of blood from the patient, subjecting it after citration to a selected band of wave lengths of ultraviolet rays, and immediately returning it to the patient. This procedure was used in 21 cases of postabortal sepsis, 17 preoperatively, and 4 postoperatively. The operation performed in every case was dilatation and curettage. Only two of the patients had received chemotherapy and in these the sulfonamide had not proved efficacious. Twelve case reports are presented, showing striking results. It is claimed that with the autotransfusion treatment the following reactions can be observed clinically:

1. Attenuation and destruction of bacteria.
2. Inactivation of toxins and viruses.
3. Increased absorption of oxygen by the blood.
4. Increase in general resistance to infection.

FRANK SPIELMAN.

Hertig, Arthur T., and Livingstone, Robert G.: Spontaneous, Threatened and Habitual Abortion: Their Pathogenesis and Treatment, New England J. Medicine 230: 797, 1944.

The authors stress the pathogenesis of spontaneous abortion, and summarize the recent literature with respect to the treatment of the theoretically preventable forms of this condition, namely, threatened and habitual abortion.

The study is based on the analysis of 1,000 spontaneous abortions. A threatened abortion as defined by Rutherford requires that the patient pass an amount of blood by vagina, excluding cervical and vaginal lesions, sufficient to make a stain 5 cm. in diameter on a vulvar pad before the case was classified as a threatened abortion. The proportion of habitual abortion in all spontaneous abortions probably lies somewhere between 3.16 and 9.8 per cent.

Two main factors were operating to produce a spontaneous abortion, namely, those traceable to defects or abnormalities of the ovum, and those due to maternal causes. In the former category were 617 abortions, or 61.7 per cent of the series, whereas the remaining 383, or 38.3 per cent, were in the latter category.

The data on habitual abortion are apparently as varied as those resulting in a chance or single spontaneous abortion. Treatment should begin prior to conception, because the genesis of many abortions is laid during the time before the first missed menstrual period. The same over-all treatment is indicated as is advocated for threatened abortion, because of the present lack of more specific therapeutic knowledge.

On the basis of a series of 1,000 cases examined embryologically and pathologically, approximately one-third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician.

Approximately 60 per cent of threatened abortions under adequate treatment may fail to abort.

Threatened abortion should be treated by some potent corpus luteum preparation, or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C, and K, and thyroid, in conjunction with a program of so-called "nutritional adequacy."

Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to, or coincident with, conception.

JAMES P. MARR.

Garcia, Pedro: Postabortal Peritonitis, Bol. Soc. chilena de obst. y ginec. **8**: 135, 1943.

Reviewing the records of Public Assistance Post 3 of Santiago de Chile, the author found 9 cases of postabortal peritonitis in 1942 and 10 in the first half of 1943, suggesting that the number of cases for 1943 will be at least twice that for 1942. In 1942 six patients, or 66.66 per cent, and in 1943 two, or 20 per cent, died. The same personnel was responsible for the diagnosis and surgical technique during both years. Therefore, the better results must be due to improved details in the treatment, such as intra-abdominal application of sulfonamides, prompt use of the Miller-Abbott tube, transfusion of plasma and blood, and sulfonamides by mouth and parenterally.

The importance of early diagnosis of peritonitis and of early intervention, which should be minimal, must be kept in mind. Before closing the abdomen an adequate amount of sulfanilamide must be placed in the cavity, especially in the cul-de-sac of Douglas. This is one of the most important factors in successful treatment. In addition, uninterrupted and periodic new doses of the drug must be given orally or parenterally. The Miller-Abbott tube is used to combat paralytic ileus, and the author has found it the decisive element in the improvement of some patients. It should be introduced early and by experienced persons. Transfusions of plasma are better than those of blood to combat shock. If blood must be used, transfusions must be small and repeated. The patient must be given large amounts of water and salt.

J. P. GREENHILL.

Gynecology

Williams, R. H., Weinglass, A. R., and Kay, G. A.: Thiouracil Storage in the Thyroid as Affected by Thyrotropic Hormone and Potassium Iodide, Am. J. M. Sc. **207**: 701, 1944.

Thiouracil has recently been used in the treatment of thyrotoxicosis. It leads to a fall in the basal oxygen consumption to normal levels with an associated clinical improvement, and a decrease in the protein-bound iodine content of the plasma. The effectiveness of this drug in inducing these changes is due to its inhibitory action on the production of the thyroid hormone.

In order to determine the quantity of thiouracil stored in the thyroid, five series of guinea pigs were given thiouracil either alone or in combination with thyrotropic hormone and potassium iodide, for varying periods of time. The thyrotropic hormone was administered in order to stimulate thyrotoxicosis, and the iodide in order to reproduce the treatment of the thyrotoxic patient first with iodide and then thiouracil. Thiouracil was found to be more concentrated in the thyroid of animals receiving no thyrotropic hormone than in those receiving the hormone. However, those animals receiving iodide in conjunction with thiouracil and thyrotropic hormone showed a greater concentration of the thiouracil in the thyroid than either of the other two groups. The authors conclude that thyrotropic hormone given with thiouracil is much more goitrogenic in guinea pigs than is thiouracil alone. The thyrotropic hormone tends to decrease the amount of thiouracil stored in the thyroid while potassium iodide greatly increases the quantity stored.

FRANK SPIELMAN.

Arana, Vicente Mugica: Considerations on the Pathogenesis and Diagnosis of Genital Tuberculosis, Toko-Ginecl. Practica 3: 43, 1944.

The author discusses tuberculosis localized in the tubes and the uterus.

The tubes may be infected by the circulatory and lymphatic routes and by contiguity. In recent and superficial infection, the tube is reddened, the fimbriae are infiltrated; but the most typical lesion is found in the serosa in the form of small tubercles. The chronic process assumes the form of hydrosalpinx or pyosalpinx, often bilateral and mobile because of lack of adhesions. The symptoms vary.

The uterus is one of the most frequent sites of tuberculosis of the genital apparatus, being involved in 50 per cent of the cases. The disease is secondary.

Lesions of the cervix are rare and may present the aspect of endocervicitis or of tuberculous ulcer of its vaginal portion. The posterior aspect of the cervix is more often involved than the anterior.

In general, uterine tuberculosis may occur at any age but it is more common during the period of genital activity. Symptoms vary: besides small hemorrhages and general symptoms secondary to salpingitis and peritonitis which nearly always coexist, there is sterility, 5 per cent of which is due to uterine tuberculosis.

To discover genital tuberculosis, except in case of external lesions, it is necessary to think of it, because symptoms which permit making the diagnosis are rarely encountered. Because early tuberculosis of the genitalia is secondary, careful questioning nearly always discloses the primary focus. In clear-cut cases of active primary lesion, the presence of exudate in the peritoneal cavity, bilateral pelvic masses with little pain and with exacerbations, evening temperature, relatively low leucocytosis and sedimentation rate which does not correspond to the process found should arouse suspicion of tuberculous etiology of the tubal process, especially when these symptoms occur in a virgin.

The best method to establish the diagnosis of uterine tuberculosis is from the material obtained by curettage, part being reserved for histologic examination and part for animal inoculation. Prognosis is serious as to function but benign as to life. The only active treatment is ultraviolet irradiation which gives satisfactory results. Hygiene and diet must receive consideration. Roentgen rays in small doses may be used in inoperable cases and in those rebellious to physiotherapeutic treatment.

J. P. GREENHILL.

Duran, Alfredo: Spontaneous Amputation of Ovarian Tumors, Bol. Soc. chilena de obst. y ginec. 8: 129, 1943.

The author describes three cases which occurred among 172 patients with benign tumor of the ovary hospitalized during the past eight years, an incidence of 1.7 per cent. The three cases included two cystic teratomas and one fibroma. An acute abdominal picture, which corresponded to torsion of the pedicle that caused the amputation, was present in two patients and during the course of a pregnancy eighteen months previously in the third. In all three, the amputated tumors had not undergone any changes because they had acquired important new vascular connections.

Ovarian tumors which undergo torsion are usually those of average size. Pregnancy favors torsion. From the clinical point of view it must be remembered that absence of adnexae on one side is not always congenital but may be due to torsion. Amputation sometimes occurs without symptoms. Once detached, the tumor may undergo resorption or remain in the abdominal cavity. Resorption is rare and occurs especially with cystic tumors. When the amputated tumor persists in the abdomen, it may be found on the large omentum or broad ligament, in the cul-de-sac of Douglas or the ileocecal region. If nutrition is insufficient in the new localization, regressive changes occur in the tumor (calcification, etc.). When the tumor becomes adherent to neighboring parts, new vessels are formed and it may persist indefinitely and even increase in volume. Ovarian dermoid cysts are those which are detached most easily. In rare cases the detached tumor has presented tuberculous infection or carcinomatous degeneration.

J. P. GREENHILL.

Gynecologic Operations

Schneider, Nicholas A.: A New Operation for Shortening the Round Ligaments, South. M. J. **37**: 434, 1944.

The author reports a new method of shortening the round ligaments in the correction of uterine displacement. A longitudinal incision is made along the round ligament and parallel to it. Flaps of the peritoneum are dissected back, exposing the ligament itself. The ligament is cut transversely and the proximal end ligated and carried along the distal portion of the ligament and tied to it where it emerges from the inguinal canal. In like manner the cut end of the distal portion is advanced along the proximal portion of the ligament and attached near the cornua. The ligaments then may be sutured together in their mid-portion. The peritoneum is closed over the shortened ligament.

The author recommends this operation on the basis of: (1) ease of performance, (2) preservation of normal anatomy, (3) less likelihood of intestinal complications, and (4) compatibility with pregnancy. Drawings describing the technique are presented.

WILLIAM BICKERS.

Harrell, William B., and Estevez, Rafael: Indications for Pelvioscopy in the Female, South. M. J. **37**: 415, 1944.

The pelvioscope is a diagnostic instrument which may often be substituted for exploratory laparotomy. Congenital defects such as bicornate uterus, absence of the pelvic structures, and the determination of sex in the hermaphrodite are positive indications for its use. For obtaining a biopsy of pelvic tumors, differentiation of pelvic endometriosis from other pelvic pathology, and the determination of the presence or absence of metastases, the instrument is useful. Large ovarian cysts can be aspirated. The differentiation between appendicitis and pelvic inflammation is made possible. Extrauterine pregnancies may be differentiated from other nonoperative pelvic pathology. The authors have recently used a long, dull hook for retracting the viscera and thus gaining better exposure. Sterilization by cauterization of the uterine cornua through the pelvioscope is possible. The operation is done through a small stab wound with a minimum of trauma and shock. Photographs of the instrument are presented.

WILLIAM BICKERS.

Falk, Henry C.: Cornual Resection for the Treatment of Salpingitis, West. J. Surg. **52**: 309, 1944.

Primary gonorrheal infection of the tubes occurs by direct extension along the cervical canal and endometrium. Gonorrheal endometritis can be demonstrated but is rarely diagnosed because its symptomatology is overshadowed by the salpingitis. The chronic pus tube is the result of repeated infection from the lower genital tract. In postabortal infections the bacteria enter the endometrium at the placental site and invade the parametrium by way of the lymphatics. Differentiation is made between it and gonorrheal infection by the location of the resulting inflammatory masses. In both cases the acute infection is managed conservatively. In the chronic, recurring salpingitis due to gonorrheal infection, however, surgery is indicated. The object of the surgery is to relieve symptoms and not necessarily to remove all pathology. Since the infection is seen in young women, conservation of the genital organs is desirable. Therefore, the author reports a study on 1,000 women treated by resection of the cornual ends of the tubes to prevent recurrence of the ascending infection. Clinical cures were reported in 85 per cent.

WILLIAM BICKERS.

Emmert, Frederick V.: Vaginal Hysterectomy, Surg., Gynec. and Obst. **79**: 277, 1944.

The author presents 600 cases of vaginal hysterectomy with a three-year follow-up on 502 private patients and a six-month follow-up on 98 ward cases. The

operations were done under combined local infiltration and block anesthesia. The technique of the operative procedure, which is a modification of Dickinson's operation, is well illustrated and the various stages described in detail. Briefly, it consists of a vaginal hysterectomy, advancement of the bladder above and beyond the joined stumps of the broad and round ligaments, and finally an anterior and posterior repair. The results are reported as satisfactory in 87.33 per cent of the cases. Recurrences were present in 12.66 per cent and are reported as follows:

	Cases	Per cent
Cystoceles	36	6.0
Rectoceles	28	4.6
Enteroceles	5	0.83
Incomplete vagina	5	0.83
Urethrocele	2	0.33

L. M. HELLMAN.

Borras, Pablo: Myomectomy as Conservative Surgery, Semana méd. **51**: 1334, 1944.

The author uses temporary ligation of the uterine arteries and makes an anteroposterior lozenge-shaped incision embracing the tumor zone as in fundus resection. If necessary, this incision can be prolonged; it restores normal uterine form when the organ is reconstructed. The author excises a wedge of muscle, conserving the myoperitoneal and myoendometrial planes. Then he sutures the myomucous flaps, obliterates the dead space of the extirpated tissue with a few interrupted sutures, and approximates the myoperitoneal flaps, being careful to adjust them correctly.

J. P. GREENHILL.

Labor, Management, Complications

Phaneuf, L. E.: Ruptured Uterus Following the Spinelli Operation for Inversion of the Uterus, Am. J. Surg. **56**: 379, 1942.

The patient was 30 years old and had had two forceps deliveries. Ten weeks following the termination of her second pregnancy it was discovered that she was suffering from an inversion of the uterus which the author repaired, performing a Spinelli operation. Recovery was without incident. She became gravid for the third time two years after the operation, and because of the danger of rupture of the uterus, the author planned delivery by cesarean section well before her expected date of confinement. However, three days before that date, the patient suddenly showed evidence of an acute abdominal accident, and at operation a rupture of the uterus was found for which, following removal of a living fetus, a Porro operation was done. Convalescence for both mother and baby was normal.

Pathologically, the rupture was found to have occurred along the line of previous incision in the uterus incident to the Spinelli operation. There was degeneration and rupture of the scar with digestion of collagen in this area.

FRANK SPIELMAN.

Tollefson, Donald G.: Methergine (Synthetic Lysergic Acid Derivative), a New Oxytocic, West. J. Surg. **52**: 383, 1944.

Methergine is a synthetic ergonovine whose activity on the animal and human uterus has been demonstrated. Unlike ergotamine it does not have any inhibiting effect upon the adrenaline response of isolated rabbit uteri. No evidence of toxicity has been demonstrated. In 200 patients who had received nembutal and scopolamine in amnesic doses during labor, 1 c.c. of methergine was given intravenously as soon as separation of the placenta was in progress. Action of the oxytocic was rapid, averaging 48 seconds. Estimation of the blood loss in this series was thought to average 98 c.c. During the puerperium methergine has been given in doses of 3 tablets daily and the lochia was noticeably reduced.

The author's experience with the administration intravenously immediately after delivery of the shoulders has not been good. He recommends administration immediately after spontaneous separation of the placenta has begun.

WILLIAM BICKERS.

Cooke, B. G.: Sudden Death in Labor, Brit. M. J. 1: 457, 1944.

This article consists of a detailed case report with the necropsy findings. The principal finding and the alleged cause of death was a small aorta and evidence of status lymphaticus. The author believes such a condition may account for sudden death in some cases, especially where there is shock as from a rapid labor, as in this instance.

His search of the literature failed to reveal a similar case.

FRED L. ADAIR.

Danforth, W. C.: Test of Labor, Illinois M. J. 86: 90, 1944.

The author makes a distinction between a "trial labor" and a "test labor." Both are indicated only in borderline contractions of the pelvic inlet. The importance of the use of x-ray pelvimetry is stressed and the necessity of having this done by those who are experienced in this method is emphasized. The purpose of the trial or test should be solely to determine whether or not the fetal head will enter the pelvic inlet. It, of course, has no place in contractures of the pelvic outlet. In summary, the author states "test labor must not be regarded as a substitute for careful prenatal study of any possible disproportion. There is never an excuse for clinical laziness, and most cases in which disproportion of any extent exists may be detected before labor begins. This makes it possible to use the abdominal delivery at the time of greatest safety, that is, as an elective operation. If a trial is to be had, the birth canal must be preserved from all contamination, and, in particular, no attempt at delivery from below should be made."

FRED L. ADAIR.

Roberts, Paul C.: The Use of Methergine (Synthetic Ergonovine) in the Third Stage of Labor, West. J. Surg. 52: 380, 1944.

Methergine, a new synthetic ergonovine, was administered subcutaneously to 26 cases and intravenously to 34 cases immediately after delivery of the baby. The dose was 1 c.c., which contained $\frac{2}{10}$ mg. of the drug. Careful attention was given to blood loss, reaction time, and duration of the third stage of labor. To measure the volume of blood loss, an oil silk drape was clipped above the episiotomy incision and carried to a clean receptacle, thereby forming a trough for the collection of uterine blood. The average blood loss in the methergine series was 181 c.c. and in the control series 247 c.c. The author has previously reported no reduction in blood loss following ergonovine administration. However, this can be explained by the improved technique now used for the management of the third stage. This includes immediate expression of the placenta when the first contraction is felt following intravenous medication and prompt uterine massage.

Duration of the third stage was shorter in the methergine series than in those patients receiving ergonovine. In 82 per cent the third stage was five minutes or less. The author advises manual removal of the placenta in those cases which have not delivered the placenta within twenty minutes. The reaction time following intravenous administration was thirty seconds. It differed from the ergonovine reaction in that the first contraction was very hard, and this contracted state persisted for several hours. It is emphasized that the incidence of retained placenta can be greatly reduced if expression of the placenta is accomplished within a few minutes after injection.

WILLIAM BICKERS.

McIntyre, W. Keverall: Injection of the Umbilical Vein to Prevent Postpartum Hemorrhage, M. J. Australia 2: 113, 1944.

The author has used this procedure in about 159 cases, and is convinced of its value, not only as a method of separation and delivery of a retained placenta, but more particularly as a method of preventing or minimizing postpartum hemorrhage. The author uses this method after any intrauterine manipulation. The procedure diminishes blood loss and shock, shortens the third stage, and flushes out the uterus and vagina. The solution must be injected rapidly, and the the solution must be of

such temperature that it reaches the uterus at about 115° to 120° F. At least a pint of hot normal saline solution should be injected, as the response usually begins when this amount has been reached.

WILLIAM BERMAN.

The Newborn

Macklin, Madge Thurlow: Erythroblastosis Fetalis: A Proposed Definition and Clarification of the Term, Am. J. Dis. Child. 67: 445, 1944.

The author defines erythroblastosis as a condition in which the blood of the fetus exhibits immature cells of the erythrocytic series which are not normal either as to type or as to quantity for the stage of development of the fetus.

This condition may be elicited by numerous factors, may or may not be accompanied with hemolysis, and may or may not be accompanied with extramedullary hemopoiesis. It includes hemolytic disease of the newborn as well as erythroblastosis due to factors other than hemolysis. When it is due to antigen-antibody reaction there will be hemolysis, with accumulation of iron in the fetal liver, and there will usually be persistent extramedullary hemopoiesis. This form of erythroblastosis is hemolytic disease of the newborn. In the majority of instances the hemolysis appears to be due to the Rh factor complex.

Factors such as anoxemia cause erythroblastosis as here defined, but not hemolysis.

A tentative explanation of the failure to find antibodies in the blood of the mothers of some fetuses showing erythroblastosis is advanced, based upon a supposed immaturity of the antigen as it exists in the immature red cell, with a corresponding specificity of the antibody for this particular antigen.

Another possible explanation is based on the recently discovered fact that there are at least six different Rh factors. Preparations of only the two commoner types of antigen are employed in the usual tests.

JAMES P. MARR.

Sievers, Jerome J., Knott, Leslie W., and Soloway, Herman M.: Penicillin in the Treatment of Ophthalmia Neonatorum, J. A. M. A. 125: 690, 1944.

The authors report the treatment with penicillin of eight cases of ophthalmia neonatorum. They started with 10,000 units of penicillin every three hours for a total of six doses. At first this was found to be inadequate, and was later changed so that the dosage was adjusted individually for each case. All except two of the cases responded to therapy within twenty-four hours, as manifested by subsidence of active inflammation. In the six cases that responded to the specific therapy, clinical recovery occurred in from three to six days with complete absence of purulent discharge, chemosis, and injection. The disappearance of specific organisms in smears and cultures was noted in from nine to twenty-four hours after beginning treatment with penicillin. One case developed an urticarial rash after the third injection of penicillin. The criteria of cure were (1) absence of clinical activity, (2) three negative smears of gram-negative intracellular diplococci, and (3) three negative cultures for gonococci.

WILLIAM BERMAN.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, Feb. 2, 1946, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by Nov. 1, 1945.

All candidates are now required to be out of medical school eight years, and in that time they must have completed an approved one-year internship and at least three years of approved special formal training, or its equivalent by the preceptorship method under a recognized obstetrician-gynecologist or a diplomate of this Board, in the seven years following the intern year. This Board's requirements for internships and special training are similar to those of the American Medical Association, since the Board and the American Medical Association are at present cooperating in a survey of acceptable institutions.

A number of changes in Board regulations and requirements were put into effect at the Board's last annual meeting held in June, 1945. These were designed to aid civilians as well as candidates in the Service and have been incorporated in the Bulletin of the Board, copy of which may be obtained from the Secretary's Office, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

All candidates are required to take the Part I examination which consists of a written examination and the submission of twenty-five case history abstracts, and the Part II examination which consists of an oral-clinical and pathology examination. The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1946, or early June, 1946, in that city nearest to the largest group of candidates. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

Announcement

Twenty-Fifth Anniversary Issue

The editors and publishers of the JOURNAL are preparing a special number to commemorate the completion of a quarter of a century of uninterrupted publication. This will appear in December.

Correspondence

Venous Ligation in Obstetrics

To the Editor:

The present wave of enthusiasm for prophylactic venous ligation promises to reach alarming proportions, especially in certain quarters. The time has come to introduce a note of caution regarding its obstetric application.

Recently, the writer witnessed bilateral femoral vein ligation in an apparently normal 24-year-old primipara four days post partum. At the time of operation, no clot could be aspirated from the right side. The left vein was tied without effort to establish presence or absence of thrombus. Immediately post partum, the patient, who was delivered by a member of the visiting staff, complained of difficulty turning in bed and of pain in the right leg. She was more comfortable in the erect position, and daily the ability to move improved and the leg pain diminished. There was definite pain over both sacroiliac joints posteriorly, and over the symphysis pubis. On the evening of the third day, an isolated "spike" to 101.0° F. occurred in the temperature curve. This fever lasted less than eight hours, and when the decision to ligate veins was made, the temperature was 99.0° F. and the pulse rate 80 beats a minute. So far as the writer can ascertain, the motivating factor in the decision to operate was pain in the calf of the right leg on dorsiflexion of the foot (Homan's sign). The day following operation, the temperature was 101.2° F. but returned to normal on the second postoperative day. On the third postoperative, and the seventh postpartum day, a febrile reaction began, lasted six days, and three times the temperature curve reached a peak of 102.0° F. The patient complained of numbness in both legs and there was tenderness, swelling, and redness, especially on the right. At least twice during the course of this febrile illness the patient experienced definite chills. Saphenous vein ligation was refused by the patient, who was discharged in a wheel chair on the fourteenth postpartum day. Both legs were considerably swollen six weeks post partum.

"Phlebothrombosis" or "bland" thrombosis tends to occur in patients over 40 years of age, especially after prolonged bed rest. In addition to pain in the calf of the leg, an ascending "step ladder" pulse and Homan's sign represent the principal diagnostic points. Phlebography, once popular, is employed less and less as a diagnostic measure. All writers set considerable store by Homan's sign. Allen states unequivocally that a positive Homan's sign is "pathognomonic when present" and that "if discomfort in the calf muscles or the popliteal space is experienced during this maneuver, *one can be sure* [italics mine] that deep venous thrombosis exists." Having elicited a positive Homan's sign some months ago in a pregnant woman who spent the previous day refinishing the floor of her apartment, I am inclined to believe that sore muscles may occur without necessitating a diagnosis of "bland" thrombosis.

Since all writers emphasize that "bland" thrombosis shows a definite predilection for the upper age groups (Allen's series of 202 patients showed 81 per cent over 40 years of age), and since I could not remember a single death from embolus as a sole cause in the University of Iowa series, it was decided to collect some information concerning the incidence of fatality from embolus in obstetric practice. Letters were written to the chiefs of representative clinics in various parts of the United States. Their replies were generous and prompt, and data supplied are listed in the accompanying table.

From these figures, it is apparent that the chance any pregnant woman will die from embolus is 1 in 7,101. If we consider only obstetric patients whose puerperal courses were relatively normal, and exclude histories where there were complicating factors contributory to, or productive of, death, we find only four fatalities from embolus among 139,546 patients, or 1 in 34,886! In other words, the uncomplicated obstetric patient stands only one chance in almost 35,000 of embolic death from bland thrombosis. Stated differently, phlebothrombosis is virtually nonexistent among relatively normal puerperal women.

In the light of such figures, it is difficult to believe that prophylactic venous ligation will save the lives of many obstetric patients. In fact, the patient will experience far greater

INSTITUTION	PATIENTS (NUMBER)	FATAL EMBOLUS	
		TOTAL NUMBER	NONMORBID PUERPERIUM NO ANTECEDENT COMPLICATION
St. Louis University Hospitals (Vogt)	15,095	3	*
Los Angeles County Hospital (Hanley)	46,395	6	*
St. Vincent's Hospital (L. A.) (Hanley)	12,000	0	
Chicago Lying-in (Dieckmann)	45,000	6	3
Margaret Hague (Cosgrove)	78,546	13	1
University of Iowa (Plass)	16,000	2	0
Totals	213,036	30	4

*Figures not available.

danger from the anesthetic and the operation than she will ever incur from phlebothrombosis. The obstetric patient, by and large, is a young woman. There is a growing tendency to get her out of bed early in the puerperium. The two chief causes of bland thrombosis, or phlebothrombosis, age and inactivity, are not commonly present in the obstetric patient.

There is no doubt that prophylactic venous ligation has a place in surgery and in geriatrics. I do not believe it has a place in routine obstetric practice. Enthusiasm for the new should not cause us to jettison the accumulated wisdom of the past.

(Signed) William F. Mengert, M.D.

2211 Oak Lawn Avenue
Dallas 4, Texas

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Edward A. Schumann, Philadelphia, Pa. *Secretary,* Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting cancelled.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Lewis F. Smead, Toledo, Ohio. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Dallas, Tex. Annual meeting not announced.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Annual meeting cancelled.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Philip F. Williams, Philadelphia, Pa. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallax Tex. Meeting cancelled.

New York Obstetrical Society. (1863) *President,* R. A. Hurd. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Charles A. Behney *Secretary,* John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* James E. Fitzgerald. *Secretary,* Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President* Chas W. Mueller. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Charles Hunt. *Secretary-Treasurer,* Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* James S. Taylor. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* George Van S. Smith. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Roy J. Hefferman, Brookline, Mass. *Secretary,* Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* E. L. Zander. *Secretary,* R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. (1924) *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Robert B. Kennedy. *Secretary,* Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.

Alabama Association of Obstetricians and Gynecologists. *President,* J. M. Weldon, Mobile, Ala. *Secretary,* Eva F. Dodge, Montgomery, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* Geo. D. Huff. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* A. L. Carson, Jr. *Secretary,* L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Sylvester Goodman. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held last Wednesday of each month.

Nassau Obstetrical Society. (1944) *President,* Arthur C. Martin. *Secretary,* William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Jacob Clahr. *Secretary-Treasurer,* J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino Everett. *Secretary,* H. H. Skinner, Yakima. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* J. Milton Singleton. *Secretary,* Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Frank Locke, Winston-Salem. *Secretary,* Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.